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(54) Title: COMPOUNDS FOR THE MODULATION OF PPARγ ACTIVITY

(57) Abstract: Modulators of PPARγ activity are provided which are useful in pharmaceutical compositions and methods for the treatment of conditions such as type II diabetes and obesity.

COMPOUNDS FOR THE MODULATION OF PPARγ ACTIVITY

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is related to USSN 60/073,042, filed January 29, 1998, and USSN 09/234,327, filed January 20, 1999, and claims the benefit of USSN 60/141,672, filed June 30, 1999. This application is also related to USSN _______, filed June 28, 2000, (Attorney Docket 018781-002710US), the disclosures of each of the above being incorporated herein by reference in their entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

The invention described herein was not made with the aid of any federally sponsored grants.

FIELD OF THE INVENTION

The present invention relates to compounds that modulate the PPARγ receptor and are useful in the diagnosis and treatment of type II diabetes (and complications thereof), hypercholesterolemia (and related disorders associated with abnormally high or low plasma lipoprotein or triglyceride levels) and inflammatory disorders.

BACKGROUND OF THE INVENTION

The peroxisome proliferator-activated receptors (PPARs) are transducer proteins belonging to the steroid/thyroid/retinoid receptor superfamily. The PPARs were originally identified as orphan receptors, without known ligands, but were named for their ability to mediate the plelotropic effects of fatty acid peroxisome proliferators. These receptors function as ligand-regulated transcription factors that control the expression of target genes by binding to their responsive DNA sequence as heterodimers with RXR. The target genes encode enzymes involved in lipid metabolism and differentiation of adipocytes. Accordingly, the discovery of transcription factors involved in controlling lipid metabolism has provided insight into regulation of energy homeostasis in vertebrates, and further provided targets for the development of therapeutic agents for disorders such as obesity, diabetes and dyslipidemia.

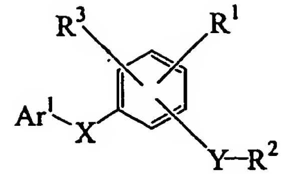
PPARγ is one member of the nuclear receptor superfamily of ligand-activated transcription factors and has been shown to be expressed in an adipose tissue-specific manner. Its expression is induced early during the course of differentiation of several preadipocyte cell lines. Additional research has now demonstrated that PPARγ plays a pivotal role in the adipogenic signaling cascade. PPARγ also regulates the ob/leptin gene which is involved in regulating energy homeostasis, and adipocyte differentiation which has been shown to be a critical step to be targeted for anti-obesity and diabetic conditions.

In an effort to understand the role of PPARγ in adipocyte differentiation, several investigators have focused on the identification of PPARγ activators. One class of compounds, the thiazolidinediones, which were known to have adipogenic effects on preadipocyte and mesenchymal stem cells *in vitro*, and antidiabetic effects in animal models of non-insulin-dependent diabetes mellitus (NIDDM) were also demonstrated to be PPARγ-selective ligands. More recently, compounds that selectively activate murine PPARγ were shown to possess *in vivo* antidiabetic activity in mice.

Despite the advances made with the thiazolidinedione class of antidiabetes agents, unacceptable side effects have limited their clinical use. Accordingly, there remains a need for potent, selective activators of PPARγ which will be useful for the treatment of NIDDM and other disorders related to lipid metabolism and energy homeostasis. Still further, compounds that block PPARγ activity would be useful for interfering with the maturation of preadipocytes into adipocytes and thus would be useful for the treatment of obesity and related disorders associated with undesirable adipocyte maturation. Surprisingly, the present invention provides compounds that are useful as activators as well as antagonists of PPARγ activity and compositions containing them, along with methods for their use.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides methods of modulating conditions which are mediated by PPARγ. The methods typically involve contacting the host with a PPARγ-modulating amount of a compound having the formula:



in which the symbol Ar^1 represents a substituted or unsubstituted aryl group; the letter X represents a divalent linkage selected from the group consisting of substituted or unsubstituted -(C_1-C_6)alkylene, substituted or unsubstituted -(C_1-C_6)alkylenoxy, substituted or unsubstituted -(C_1-C_6)alkylenamino, substituted or unsubstituted -(C_1-C_6)alkylene-$S(O)_k$-, -O-, C(O)-, N(R^{11})-, -N(R^{11})C(O)-, -$S(O)_k$- and a single bond, in which R^{11} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and aryl(C_1-C_4)alkyl and the subscript k is an integer of from 0 to 2. The letter Y, in the above formula represents a divalent linkage, in either orientation, selected from the group consisting of substituted or unsubstituted (C_1-C_6)alkylene, -O-, -C(O)-, -N(R^{12})-$S(O)_m$-, -N(R^{12})C(O)-, -N(R^{12})-$S(O)_m$-(R^{13})-, -$S(O)_n$-, a single bond, and combinations thereof in which R^{12} and R^{13} are members independently selected from the group consisting of hydrogen, substituted or unsubstituted (C_1-C_8)alkyl, substituted or unsubstituted (C_2-C_8)heteroalkyl and aryl(C_1-C_4)alkyl; and the subscripts m and n are independently integers of from 0 to 2.

The symbol R^1 represents a member selected from hydrogen, halogen, cyano, nitro, (C_1-C_8)alkyl, (C_1-C_8)alkoxy, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -C(O)R^{14}, -$S(O)_p$-R^{14}, -$S(O)_q$-$NR^{15}R^{16}$, -O-C(O)-OR^{17}, -O-C(O)-R^{17}, -O-C(O)-$NR^{15}R^{16}$, -N(R^{14})-C(O)-$NR^{15}R^{16}$, -N(R^{14})-C(O)-R^{17} and –N(R^{14})-C(O)-OR^{17}, in which R^{14} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl; R^{15} and R^{16} are members independently selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl, and aryl(C_1-C_4)alkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; and R^{17} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl. In each of the descriptions of, for example, alkyl, alkoxy and heteroalkyl, the groups can be substituted or unsubstituted.

The symbol R^2 represents a substituted or unsubstituted aryl group. Preferably, R^2 represents a phenyl, naphthyl, pyridazinyl or pyridyl group. More preferably, R^2 is a phenyl, naphthyl, pyridazinyl or pyridyl group substituted with from 0-3 substituents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -CN, -CF_3, -C(O)-(C_1-C_8)alkyl, -(C_1-C_8)alkyl and -NH_2. While certain preferred substituents have been provided (e.g., -OCF_3 and -CF_3), the terms alkyl and alkoxy are also meant to include

substituted versions thereof, preferably halosubstituted versions including those specifically noted.

The symbol R^3 represents a halogen, cyano, nitro or a substituted or unsubstituted (C_1-C_8)alkoxy group, preferably a halogen, cyano or (C_1-C_4)alkoxy group. Most preferably, halogen, methoxy or trifluoromethoxy.

In another aspect, the present invention provides compounds of the formula above, as well as pharmaceutical compositions containing the compounds described above.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions:

The following abbreviations are used herein: PPARγ: peroxisome proliferator-activated receptor γ; NIDDM: non-insulin-dependent diabetes mellitus; Et_3N: triethylamine; MeGH: methanol; and DMSO: dimethylsulfoxide.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated *(i.e.* C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)ethyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as "heteroalkyl," "cycloalkyl" and "alkylene." The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower

alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms are optionally oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Also included in the term "heteroalkyl" are those radicals described in more detail below as "heteroalkylene" and "heterocycloalkyl." The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini. Still further, for alkylene and heteroalkylene linking groups, as well as all other linking group provided in the present invention, no orientation of the linking group is implied.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1 -(1,2,5,6-tetrahydropyridyl), 1 -piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

Additionally, terms such as "fluoroalkyl," are meant to include monofluoroalkyl and polyfluoroalkyl.

The term "aryl," employed alone or in combination with other terms *(e.g.,* aryloxy, arylthioxy, arylalkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The rings may each contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The aryl groups that contain heteroatoms may be referred to as "heteroaryl" and can be attached to the remainder of the molecule through a heteroatom Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-benzothiazolyl, 5-benzothiazolyl, 2-benzoxazolyl, 5-benzoxazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolinyl, 5-isoquinolinyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolinyl, and 6-quinolinyl. Substituents for each of the above noted aryl ring systems are selected from the group of acceptable substituents described below. The term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) or a heteroalkyl group (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

Each of the above terms (*e.g.*, "alkyl," "heteroalkyl" and "aryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR''C(O)_2R'$, $-NH-C(NH_2)=NH$, $-NR'C(NH_2)=NH$, $-NH-C(NH_2)=NR'$, -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R''$, -CN and $-NO_2$ in a number ranging from zero to (2N+1), where N is the total number of carbon atoms in such radical. R', R" and R"' each independently refer to hydrogen, unsubstituted(C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups,

or aryl-(C_1-C_4)alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., -$C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like). Preferably, the alkyl groups (and related alkoxy, heteroalkyl, etc.) are unsubstituted or have 1 to 3 substituents selected from halogen, -OR', =O, -NR'R", -SR', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -NR"C(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -CN and $-NO_2$. More preferably, the alkyl and related groups have 0, 1 or 2 substituents selected from halogen, -OR', =O, -NR'R", -SR', $-CO_2R'$, -CONR'R", -NR"C(O)R', -CN and $-NO_2$.

Similarly, substituents for the aryl groups are varied and are selected from halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$- $-CO_2R'$, -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', $-NR"C(O)_2R'$, -NR'-C(O)NR"R"', $-NH-C(NH_2)=NH$, $-NR'C(NH_2)=NH$, $-NH-C(NH_2)=NR'$, -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-N_3$, $-CH(Ph)_2$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, (unsubstituted aryl)-(C_1-C_4)alkyl, and (unsubstituted aryl)oxy-(C_1-C_4)alkyl. Preferably, the aryl groups are unsubstituted or have from 1 to 3 substituents selected from halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$- $-CO_2R'$, -CONR'R", -C(O)R', -NR"C(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl. Still more preferably, the aryl groups have 0, 1 or 2 substituents selected from halogen, -OR', -NR'R", -SR', -R', -CN, $-NO_2$- $-CO_2R'$, -CONR'R", -NR"C(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl.

Two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula wherein T and U are independently -NH-, -O-, $-CH_2$- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently $-CH_2$-, -O-, -NH-, -S-, -S(O)-, $-S(O)_2$-, $-S(O)_2NR'$- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula $-(CH_2)_s-X-(CH_2)_t-$, where s

and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituent R' in -NR'- and $-S(O)_2NR'-$ is selected from hydrogen or unsubstituted (C_1-C_6)alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science,* 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

General:

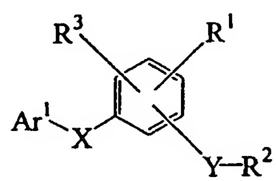
A new class of compounds that interact with PPARγ has now been discovered. Depending on the biological environment *(e.g.*, cell type, pathological condition of the host, *etc.*), these compounds can activate or block the actions of PPARγ. By activating the PPARγ receptor, the compounds will find use as therapeutic agents capable of modulating conditions mediated by the PPARγ receptor. As noted above, example of such conditions is NIDDM. Additionally, the compounds are useful for the prevention and treatment of complications of diabetes (*e.g.*, neuropathy, retinopathy,

glomerulosclerosis, and cardiovascular disorders), and treating hyperlipidemia. Still further, the compounds are useful for the modulation of inflammatory conditions which most recently have been found to be controlled by PPARγ (see, Ricote, *et al., Nature,* 391:79-82 (1998) and Jiang, *et al., Nature,* 391:82-86 (1998). Examples of inflammatory conditions include rheumatoid arthritis and atherosclerosis.

Compounds that act via antagonism of PPARγ are useful for treating obesity, hypertension, hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, and metabolic disorders.

__Embodiments of the Invention__:

In one aspect, the present invention provides compounds which are represented by the formula:



(I)

In formula (I), the symbol Ar^1 represents a substituted or unsubstituted aryl group. Preferably, Ar^1 is a monocyclic or fused bicyclic aryl group having from zero to four heteroatoms as ring members. More preferably, Ar^1 is a monocyclic or fused bicyclic aryl group comprising two fused six-membered rings, two fused five-membered rings, or a six-member ring having a fused five-membered ring. heteroaryl group containing from 1 to 3 nitrogen atoms in the ring or rings. Particularly preferred embodiments are those in which Ar^1 is phenyl, naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-quinolinyl, 3-quinolinyl, 4-isoquinolinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, 3-pyrazolyl, 2-phenyl-4-isoxazolyl and the like. Ar^1 can be both unsubstituted and substituted. In preferred embodiments, Ar^1 is substituted with from 0 to 3 substituents selected from halogen, $-OCF_3$, -OH, -O-(C_1-C_6)alkyl, $-CF_3$, (C_1-C_6)alkyl, or $-NO_2$. In one group of preferred embodiments, Ar^1 is a monocyclic heteroaryl group containing 1 to 2 nitrogen atoms in the ring and being monosubstituted by halogen, $-OCF_3$ or $-CF_3$. In another group of preferred embodiments, Ar^1 is a phenyl or naphthyl group having from 1 to 3 substituents selected from halogen, cyano, nitro, (C_1-C_8)alkyl or (C_1-C_8)alkoxy.

The letter X represents a divalent linkage selected from substituted or unsubstituted $(C_1\text{-}C_6)$alkylene, substituted or unsubstituted $(C_1\text{-}C_6)$alkylenoxy, substituted or unsubstituted $(C_1\text{-}C_6)$alkylenamino, substituted or unsubstituted $(C_1\text{-}C_6)$alkylene-$S(O)_k$, -O-, -C(O)-, -$N(R^{11})$-, -$N(R^{11})C(O)$-, -$S(O)_k$- and a single bond, in which R^{11} is a member selected from hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl and aryl$(C_1\text{-}C_4)$alkyl and the subscript k is an integer of from 0 to 2. In preferred embodiments, X represents -O-, -C(O)-, substituted or unsubstituted $(C_1\text{-}C_6)$alkylene, -$N(R^{11})$-, or -$S(O)_k$-. Most preferably, X represents -O-, -CH_2-, -$CH(CH_3)$-, -$CH(CH_2CH_3)$-, -CH(isopropyl)-, -CH(CN)-, -C(O)-, -$N(R^{11})$-, or -$S(O)_k$-. Still further preferred are those embodiments in which X represents -O-, -CH_2-, -$CH(CH_3)$-, -C(O)-, -$N(R^{11})$-, or -$S(O)_k$-, wherein R^{11} is hydrogen, methyl, ethyl, propyl and isopropyl.

The letter Y, in the above formula represents a divalent linkage selected from substituted or unsubstituted $(C_1\text{-}C_6)$alkylene, -O-, -C(O)-, -$N(R^{12})$-$S(O)_m$-, -$N(R^{12})$-$S(O)_m$-$N(R^{13})$-, -$N(R^{12})C(O)$-, -$S(O)_n$-, a single bond, and combinations thereof, in which R^{12} and R^{13} are members independently selected from hydrogen, substituted or unsubstituted $(C_1\text{-}C_8)$alkyl, substituted or unsubstituted $(C_2\text{-}C_8)$heteroalkyl and substituted or unsubstituted aryl$(C_1\text{-}C_4)$alkyl; and the subscripts m and n are independently integers of from 0 to 2. In preferred embodiments, Y represents -$N(R^{12})$-$S(O)_2$- or -$N(R^{12})$-C(O)-. More preferably, Y represents -$N(R^{12})$-$S(O)_2$- in which R^{12} is hydrogen or substituted or unsubstituted $(C_1\text{-}C_8)$alkyl. Most preferably, Y represents -NH-$S(O)_2$-. Additionally, the linkages provided herein (represented by X and Y) can be in either orientation. More particularly, for example, the nitrogen atom of -$N(R^{12})$-$S(O)_2$- can be attached to either the central benzene ring or to the R^2 group.

The symbol R^1 represents a member selected from hydrogen, halogen, cyano, nitro, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy, -CO_2R^{14}, -$C(O)NR^{15}R^{16}$, -$C(O)R^{14}$, -$S(O)_p$-R^{14}, -$S(O)_q$-$NR^{15}R^{16}$, -O-C(O)-OR^{17}, -O-C(O)-R^{17}, -O-C(O)-$NR^{15}R^{16}$, -$N(R^{14})$-C(O)-$NR^{15}R^{16}$, -$N(R^{14})$-C(O)-R^{17} and –$N(R^{14})$-C(O)-OR^{17}, in which R^{14} is a member selected from hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl, aryl and aryl$(C_1\text{-}C_4)$alkyl; R^{15} and R^{16} are members independently selected from hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl, aryl, and aryl$(C_1\text{-}C_4)$alkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; and R^{17} is a member selected from hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl, aryl and aryl$(C_1\text{-}C_4)$alkyl. In each of the descriptions of, for example, alkyl, alkoxy and heteroalkyl, the groups can be substituted or unsubstituted. Preferably, when substituted the substituents are halogen (e.g., -CF_3, -OCF_3). In preferred

embodiments, R^1 represents hydrogen, halogen, cyano, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy, -CO_2R^{14} and -C(O)$NR^{15}R^{16}$. More preferably, R^1 represents hydrogen, halogen, cyano, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy, -CO_2R^{14} and -C(O)$NR^{15}R^{16}$ in which R^{14} is $(C_1\text{-}C_8)$alkyl, and R^{15} and R^{16} are independently hydrogen or $(C_1\text{-}C_8)$alkyl, or taken together with the nitrogen to which each is attached form a 5- or 6-membered ring. Other preferred R^1 groups are discussed below with reference to groupings of compounds wherein Ar^1 is phenyl, pyridyl, naphthyl, quinolinyl, isoquinolinyl, benzoxazolyl, benzothiazolyl and benzimidazolyl.

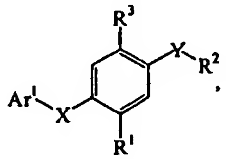
The symbol R^2 represents a substituted or unsubstituted aryl group. Preferably, R^2 represents a phenyl, naphthyl, pyridazinyl or pyridyl group. More preferably, R^2 is a phenyl, naphthyl, pyridazinyl or pyridyl group substituted with from 0-3 substituents selected from halogen, -OCF_3, -OH, -O$(C_1\text{-}C_8)$alkyl, -CN, -CF_3, -C(O)-$(C_1\text{-}C_8)$alkyl, -$(C_1\text{-}C_8)$alkyl and -NH_2. While certain preferred substituents have been provided (e.g., -OCF_3 and -CF_3), the terms alkyl and alkoxy are also meant to include substituted versions thereof, preferably halosubstituted versions including those specifically noted.

The symbol R^3 represents a halogen, cyano, nitro or a substituted or unsubstituted $(C_1\text{-}C_8)$alkoxy group, preferably a halogen, cyano or $(C_1\text{-}C_4)$alkoxy group. Most preferably, halogen, methoxy or trifluoromethoxy.

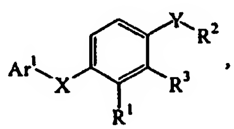
A number of preferred embodiments are provided herein. For example, in one preferred embodiment, X is a divalent linkage selected from –CH_2-, -$CH(CH_3)$-, -O-, -C(O)-, -$N(R^{11})$- and –S-; and Y is -$N(R^{12})$-$S(O)_2$-, wherein R^{12} is a member selected from hydrogen and $(C_1\text{-}C_8)$alkyl. In another preferred embodiment, X is a divalent linkage selected from –CH_2-, -$CH(CH_3)$-, -O-, -C(O)-, -$N(R^{11})$- and –S-; Y is -$N(R^{12})$-$S(O)_2$-, wherein R^{12} is a member selected from hydrogen and $(C_1\text{-}C_8)$alkyl; and R^2 is a substituted or unsubstituted aryl selected from phenyl, pyridyl, naphthyl and pyridazinyl. In yet another preferred embodiment, X is a divalent linkage selected from –CH_2-, -$CH(CH_3)$-, -O-, -C(O)-, -$N(R^{11})$- and –S-; Y is -$N(R^{12})$-$S(O)_2$-, wherein R^{12} is a member selected from hydrogen and $(C_1\text{-}C_8)$alkyl; R^2 is a substituted or unsubstituted aryl selected from phenyl, pyridyl, naphthyl and pyridazinyl; and Ar^1 is a substituted or unsubstituted aryl selected from pyridyl, phenyl, naphthyl, quinolinyl, isoquinolinyl, benzoxazolyl, benzothiazolyl, and benzimidazolyl.

One of skill in the art will understand that a number of structural isomers are represented by formula I. In one group of embodiments, the isomers are those in

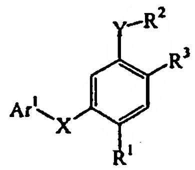
which the groups on the phenyl ring occupy positions that are not contiguous. In other embodiments, the compounds are those having the structural orientations represented by the formulae:



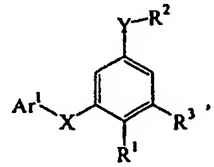
(Ia)



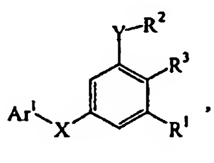
(Ib)



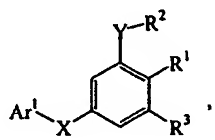
(Ic)



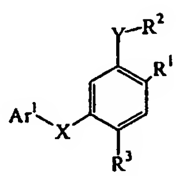
(Id)



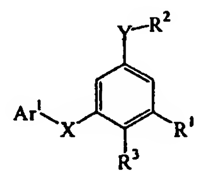
(Ie)



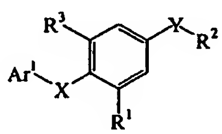
(If)



(Ig)

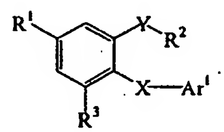


(Ih)



(Ii)

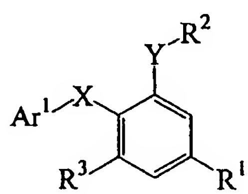
and



(Ij)

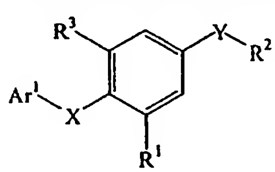
Still further preferred are those compounds having the structural orientation represented by formula Ia or Ib. Still other preferred compounds, are those of formula Ia or Ib in which the positions of R^1 and R^3 are switched (or reversed).

Yet other preferred compounds are those in which Ar^1-X- and -Y-R^2 occupy positions ortho to one another (exemplified by Ij).



(Ij)

Still another group of preferred compounds are represented by the formula:



(Ii)

Ar[1] is substituted or unsubstituted phenyl

In one group of particularly preferred embodiments, Ar^1 is a substituted or unsubstituted phenyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -$C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, -$C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar^1 is substituted or unsubstituted phenyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from $-CH_2-$, $-CH(CH_3)-$, -O-, -C(O)-, $-N(R^{11})-$ and –S-, wherein R^{11} is a member selected from hydrogen and (C_1-C_8)alkyl; Y is a divalent linkage selected from $-N(R^{12})-S(O)_2-$, wherein R^{12} is a member selected from hydrogen and (C_1-C_8)alkyl; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$, $-S(O)_q-NR^{15}R^{16}$, $-O-C(O)-R^{17}$, and $-N(R^{14})-C(O)-R^{17}$, wherein R^{14} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl; R^{15} and R^{16} are members independently selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R^{17} is a member selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R^2 is a substituted or unsubstituted phenyl; and R^3 is a halogen or (C_1-C_8)alkoxy.

In further preferred embodiments, X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar^1 is a phenyl group having from 1 to 3 substituents selected from halogen, $-OCF_3$, -OH, $-O(C_1-C_6)$alkyl, $-CF_3$, (C_1-C_8)alkyl and $-NO_2$; R^1 is a member selected from halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and

(C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$, more preferably 1 to 3 substituents selected from halogen, $-OCF_3$ and $-CF_3$; and R^3 is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from halogen, $-OCF_3$, and $-CF_3$.

<u>Ar^1 is substituted or unsubstituted pyridyl</u>

In one group of particularly preferred embodiments, Ar^1 is a substituted or unsubstituted pyridyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar^1 is substituted or unsubstituted pyridyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from $-CH_2-$, $-CH(CH_3)-$, -O-, -C(O)-, $-N(R^{11})-$ and –S-, wherein R^{11} is a member selected from hydrogen and (C_1-C_8)alkyl; Y is a divalent linkage selected from $-N(R^{12})-S(O)_2-$, wherein R^{12} is a member selected from hydrogen and (C_1-C_8)alkyl; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$, $-S(O)_q-NR^{15}R^{16}$, $-O-C(O)-R^{17}$, and $-N(R^{14})-C(O)-R^{17}$, wherein R^{14} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl; R^{15} and R^{16} are members independently selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R^{17} is a member selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R^2 is a substituted or unsubstituted phenyl; and R^3 is a halogen or (C_1-C_8)alkoxy.

In further preferred embodiments, X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, $-OCF_3$, -OH, $-O(C_1-$

C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar^1 is a pyridyl group having from 0 to 3 substituents selected from halogen, -OCF_3, -OH, -O(C_1-C_6)alkyl, -CF_3, (C_1-C_8)alkyl and -NO_2; R^1 is a member selected from halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2, more preferably 1 to 3 substituents selected from halogen, -OCF_3 and –CF_3; and R^3 is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from halogen, -OCF_3, and -CF_3. Most preferably, Ar^1 is a 3-pyridyl group having preferred substituents as indicated above.

In still other particularly preferred embodiments, the compounds are represented by formula I, in which Ar^1 is a pyridyl ring having a single substituent selected from halogen, -OCF_3 and -CF_3; X is a divalent linkage selected from the group of -O-, -C(O)-, -CH_2- and combinations thereof; Y is a divalent linkage selected from the group of -NH-S$(O)_2$- and -NH-C(O)-; R^1 is selected from hydrogen, halogen, cyano, (C_1-C_8)alkyl, (C_1-C_8)alkoxy and -C(O)$NR^{15}R^{16}$ in which R^{15} and are selected from hydrogen, (C_1-C_8)alkyl, aryl and aryl(C_1-C_4)alkyl; R^2 is a phenyl or pyridyl ring, optionally substituted by 0-3 groups selected from halogen, (C_1-C_8)alkyl, -O-(C_1-C_8)alkyl and -CN; and R^3 is halogen, cyano or (C_1-C_4)alkoxy.

<u>Ar^1 is substituted or unsubstituted naphthyl</u>

In one group of particularly preferred embodiments, Ar^1 is a substituted or unsubstituted naphthyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar^1 is substituted or unsubstituted naphthyl, are those that are represented by either of formulae Ii or Ij. In this

group of embodiments, X is a divalent linkage selected from $-CH_2-$, $-CH(CH_3)-$, -O-, -C(O)-, $-N(R^{11})-$ and –S-, wherein R^{11} is a member selected from hydrogen and (C_1-C_8)alkyl; Y is a divalent linkage selected from $-N(R^{12})-S(O)_2-$, wherein R^{12} is a member selected from hydrogen and (C_1-C_8)alkyl; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$, $-S(O)_q-NR^{15}R^{16}$, $-O-C(O)-R^{17}$, and $-N(R^{14})-C(O)-R^{17}$, wherein R^{14} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl; R^{15} and R^{16} are members independently selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R^{17} is a member selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R^2 is a substituted or unsubstituted phenyl; and R^3 is a halogen or (C_1-C_8)alkoxy.

In further preferred embodiments, X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar^1 is a naphthyl group having from 0 to 3 substituents selected from halogen, $-OCF_3$, -OH, $-O(C_1-C_6)$alkyl, $-CF_3$, (C_1-C_8)alkyl and $-NO_2$; R^1 is a member selected from halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$, more preferably 1 to 3 substituents selected from halogen, $-OCF_3$ and $-CF_3$; and R^3 is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from halogen, $-OCF_3$, and $-CF_3$.

Ar^1 is substituted or unsubstituted benzothiazolyl

In another group of particularly preferred embodiments, Ar^1 is a substituted or unsubstituted benzothiazolyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, $(C_2-$

C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)N$R^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-N$R^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar^1 is substituted or unsubstituted benzothiazolyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from –CH_2-, -CH(CH_3)-, -O-, -C(O)-, -N(R^{11})- and –S-, wherein R^{11} is a member selected from hydrogen and (C_1-C_8)alkyl; Y is a divalent linkage selected from -N(R^{12})-$S(O)_2$-, wherein R^{12} is a member selected from hydrogen and (C_1-C_8)alkyl; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)N$R^{15}R^{16}$, -$S(O)_p$-R^{14}, -$S(O)_q$-N$R^{15}R^{16}$, -O-C(O)-R^{17}, and -N(R^{14})-C(O)-R^{17}, wherein R^{14} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl; R^{15} and R^{16} are members independently selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R^{17} is a member selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R^2 is a substituted or unsubstituted phenyl; and R^3 is a halogen or (C_1-C_8)alkoxy.

In further preferred embodiments, X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)N$R^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-N$R^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar^1 is a benzothiazolyl group having from 1 to 3 substituents selected from halogen, -OCF_3, -OH, -O(C_1-C_6)alkyl, -CF_3, (C_1-C_8)alkyl and -NO_2; R^1 is selected from halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2, more preferably 1 to 3 substituents selected from halogen, -OCF_3 and –CF_3; and R^3 is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from halogen, -OCF_3, and -CF_3. In particularly preferred embodiments, the benzothiazolyl group is a 2-benzothiazolyl group.

Ar^1 is substituted or unsubstituted benzoxazolyl

In another group of particularly preferred embodiments, Ar^1 is a substituted or unsubstituted benzoxazolyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar^1 is substituted or unsubstituted benzoxazolyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from –CH_2-, -$CH(CH_3)$-, -O-, -C(O)-, -N(R^{11})- and –S-, wherein R^{11} is a member selected from hydrogen and (C_1-C_8)alkyl; Y is a divalent linkage selected from -N(R^{12})-$S(O)_2$-, wherein R^{12} is a member selected from hydrogen and (C_1-C_8)alkyl; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14}, -$S(O)_q$-$NR^{15}R^{16}$, -O-C(O)-R^{17}, and -N(R^{14})-C(O)-R^{17}, wherein R^{14} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl; R^{15} and R^{16} are members independently selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R^{17} is a member selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R^2 is a substituted or unsubstituted phenyl; and R^3 is a halogen or (C_1-C_8)alkoxy.

In further preferred embodiments, X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)- (C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar^1 is a benzoxazolyl group having from 0 to 3 substituents selected from halogen, -OCF_3, -OH, -O(C_1-C_6)alkyl, -CF_3, (C_1-C_8)alkyl and -NO_2; R^1 is selected from halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -

OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2, more preferably 1 to 3 substituents selected from halogen, -OCF_3 and –CF_3; and R^3 is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from halogen, -OCF_3, and -CF_3. In particularly preferred embodiments, the benzoxazolyl group is a 2-benzoxazolyl group.

<u>Ar^1 is substituted or unsubstituted benzimidazolyl</u>

In another group of particularly preferred embodiments, Ar^1 is a substituted or unsubstituted benzimidazolyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar^1 is substituted or unsubstituted benzimidazolyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from –CH_2-, -$CH(CH_3)$-, -O-, -C(O)-, -N(R^{11})- and –S-, wherein R^{11} is a member selected from hydrogen and (C_1-C_8)alkyl; Y is a divalent linkage selected from -N(R^{12})-$S(O)_2$-, wherein R^{12} is a member selected from hydrogen and (C_1-C_8)alkyl; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14}, -$S(O)_q$-$NR^{15}R^{16}$, -O-C(O)-R^{17}, and -N(R^{14})-C(O)-R^{17}, wherein R^{14} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl; R^{15} and R^{16} are members independently selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R^{17} is a member selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R^2 is a substituted or unsubstituted phenyl; and R^3 is a halogen or (C_1-C_8)alkoxy.

In further preferred embodiments, X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-

C_8)alkyl, -C(O)- (C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar^1 is a benzimidazolyl group having from 0 to 3 substituents selected from halogen, -OCF_3, -OH, -O(C_1-C_6)alkyl, -CF_3, (C_1-C_8)alkyl and -NO_2; R^1 is selected from halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1- C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2, more preferably 1 to 3 substituents selected from halogen, -OCF_3 and –CF_3; and R^3 is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from halogen, -OCF_3, and -CF_3. In particularly preferred embodiments, the benzimidazolyl group is a 2-benzimidazolyl group.

<u>Ar^1 is substituted or unsubstituted quinolinyl or isoquinolinyl</u>

In another group of particularly preferred embodiments, Ar^1 is a substituted or unsubstituted quinolinyl or isoquinolinyl group. Further preferred are those embodiments in which the compound is represented by any of formulae Ia through Ij. Still further preferred are those embodiments in which X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

Other particularly preferred embodiments wherein Ar^1 is substituted or unsubstituted quinolinyl or isoquinolinyl, are those that are represented by either of formulae Ii or Ij. In this group of embodiments, X is a divalent linkage selected from –CH_2-, -CH(CH_3)-, -O-, -C(O)-, -N(R^{11})- and –S-, wherein R^{11} is a member selected from hydrogen and (C_1-C_8)alkyl; Y is a divalent linkage selected from -N(R^{12})-$S(O)_2$-, wherein R^{12} is a member selected from hydrogen and (C_1-C_8)alkyl; R^1 is a member selected from hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14}, -$S(O)_q$-$NR^{15}R^{16}$, -O-C(O)-R^{17}, and -N(R^{14})-C(O)-R^{17}, wherein R^{14} is a member selected from hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl; R^{15} and R^{16} are members independently selected from hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the

nitrogen to which each is attached form a 5-, 6- or 7-membered ring; R^{17} is a member selected from hydrogen, $(C_1$-$C_8)$alkyl and $(C_2$-$C_8)$heteroalkyl; the subscript p is an integer of from 0 to 2; the subscript q is 2; R^2 is a substituted or unsubstituted phenyl; and R^3 is a halogen or $(C_1$-$C_8)$alkoxy.

In further preferred embodiments, X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from hydrogen, halogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$heteroalkyl, $(C_1$-$C_8)$alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O$(C_1$-$C_8)$alkyl, -C(O)- $(C_1$-$C_8)$alkyl, -CN, -CF_3, $(C_1$-$C_8)$alkyl and -NH_2; and R^3 is selected from halogen, methoxy and trifluoromethoxy.

In still further preferred embodiments, Ar^1 is a quinolinyl or isoquinolinyl group having from 0 to 3 substituents selected from halogen, -OCF_3, -OH, -O$(C_1$-$C_6)$alkyl, -CF_3, $(C_1$-$C_8)$alkyl and -NO_2; R^1 is selected from halogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$heteroalkyl and $(C_1$- $C_8)$alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from halogen, -OCF_3, -OH, -O$(C_1$-$C_8)$alkyl, -C(O)-$(C_1$-$C_8)$alkyl, -CN, -CF_3, $(C_1$-$C_8)$alkyl and -NH_2, more preferably 1 to 3 substituents selected from halogen, -OCF_3 and –CF_3; and R^3 is selected from halogen, methoxy and trifluoromethoxy. Yet further preferred embodiments are those in which R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from halogen, -OCF_3, and -CF_3. In particularly preferred embodiments, the quinolinyl or isoquinolinyl group is selected from 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 3-isoquinolinyl and 4-isoquinolinyl groups.

In another aspect, the present invention provides pharmaceutical compositions comprising at least one of the above compounds in admixture with a pharmaceutically acceptable excipient.

In yet another aspect, the present invention provides methods for modulating conditions mediated by PPARγ in a host. More particularly, the conditions are selected from non-insulin-dependent diabetes mellitus, obesity, conditions associated with abnormal plasma levels of lipoproteins or triglycerides, and inflammatory conditions such as, for example, rheumatoid arthritis and atherosclerosis.

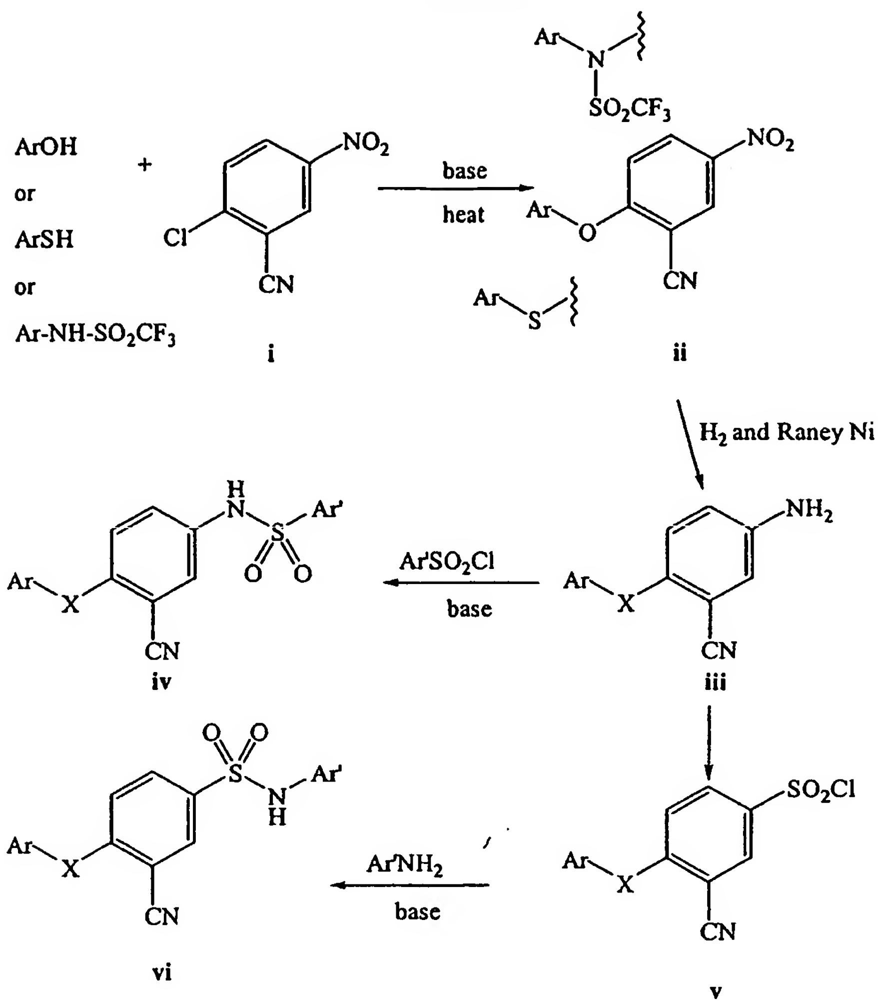
<u>Preparation of the Compounds</u>

The compounds of the present invention can be prepared using standard synthetic methods. For exemplary purposes, Scheme 1 illustrates methods for the

preparation of compounds of structural formula (Ia). One of skill in the art will understand that similar methods can be used for the synthesis of compounds in the other structural classes.

As shown in Scheme 1, compounds of the present invention can be prepared beginning with commercially available 2-chloro-5-nitrobenzonitrile (i). Treatment of J with a phenol, thiophenol, or optionally protected aniline in the presence of base and heat provides the adduct (ii). Reduction of the nitro group in ii with, for example, H_2 in the presence of Raney nickel catalyst provides an aniline derivative (iii). Sulfonylation of iii with an appropriate arylsulfonyl halide (Ar^1 50_2C_1) in the presence of base (typically a tertiary amine) provides a target compound (iv). Compound iii can also be converted to a related compound of formula (vi) in which the orientation of the sulfonamide linkage is reversed. Thus, conversion of the aniline iii to the benzenesulfonyl chloride v can be accomplished using methods described in Hoffman, Organic Syntheses Collective Volume VII, p. 508-511. Subsequent treatment of v with an appropriate aniline provides the target compound vi.

Scheme 1



Other compounds of the present invention can be prepared beginning with, for example, 3 ,4-difluoronitrobenzene, 3-chloro-4-fluoronitrobenzene, 2-chloro-5-nitroanisole, 3-bromo-4-fluoronitrobenzene and the like.

Analysis of the Compounds

The compounds of the present invention can be evaluated for modulation of the PPARγ receptor using assays such as those described in Jiang, *et al., Nature* **391**:82-86 (1998), Ricote, *et al., Nature* **391**:79-82 (1998) and Lehmann, *et al., J. Biol. Chem.* **270**(12): 12953-12956 (1995). Alternatively, the compounds can be evaluated for their ability to displace radiolabeled BRL 49653 from a PPARγ-GST fusion protein as follows:

Materials:

PPARγ-GST fusion protein (prepared according to standard procedures), [^{3}H]-BRL 49653 having 50 Ci/mmol specific activity, Polyfiltronics Unifilter 350 filtration plate and glutathione-Sepharose® beads (from Pharmacia: washed twice with l0x binding buffer in which BSA and DTI can be left out).

Method:

Binding buffer (10 mM Tris-HCl, pH 8.0, 50 mM KCI, 10 mM DTT, 0.02% BSA and 0.0 1% NP-40) is added in 80 microliter amounts to the wells of the filtration plate. The test compound is then added in 10 microliters of DMSO. The PPARγ-GST fusion protein and radiolabeled BRL compound are premixed in binding buffer containing 10 mM DTT and added in 10 microliter amounts to the wells of the plate to provide final concentrations of 1 μg/well of PPARγ-GST fusion protein and 10 nM [^{3}H]-BRL 49653 compound. The plate is incubated for 15 minutes. Glutathione-agarose bead is added in 50 μL of binding buffer, and the plate is vigorously shaken for one hour. The plate is washed four times with 200 μL/well of binding buffer (without BSA and DTT). The bottom of the plate is sealed and 200 μL/well of scintillation cocktail is added. The top of the plate is then sealed and the radioactivity is determined.

Formulation and Administration of the Compounds (Compositions)

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. Accordingly, the present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and either a compound of formula (I) or a pharmaceutically acceptable salt of a compound of formula (I).

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as

diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1000 mg, preferably 1.0 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use for the treatment of obesity, NIDDM, or inflammatory conditions, the compounds utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.001 mg/kg to about 100 mg/kg daily. A daily dose range of about 0.1 mg/kg to about 10 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following examples are offered by way of illustration and are not intended to limit the scope of the invention.

EXAMPLES

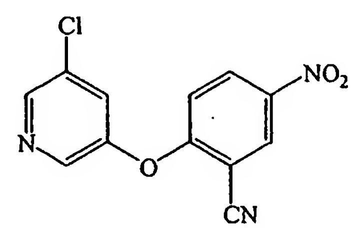
Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^{1}H-NMR spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Electron Ionization (EI) mass spectra were recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). In tables, a single m/e value is reported for the M+H (or as noted M-H) ion containing the most common atomic

isotopes. Isotope patterns correspond to the expected formula in all cases. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard 1100 MSD electrospray mass spectrometer using the HP1 100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.lmg/mL and 1 microliter was infused with the delivery solvent into the mass spectrometer which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using 1:1 acetonitrile/water with 1% acetic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2mM NH_4OAc in acetonitrile/water as delivery solvent.

Abbreviations: N-hydroxybenzotriazole (HOBT), 2-(1H-benzotriazole-1-yl)- 1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), N-methylmorpholine (NMM),:1-hydroxy-7-azabenzotriazole (HOAT), O-(7-azabenzotriazole-1-yl)-N,N,N' ,N'--tetramethyluronium hexafluorophosphate (HATU), 1-(3 -dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI).

EXAMPLE 1

This example illustrates the preparation of 5-nitro-2-(3-chloro-5-pyridyloxy)benzonitrile (1.1).



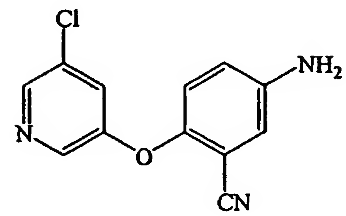
1.1

To a solution of 2-chloro-5-nitrobenzonitrile (18.3 g, 100 mmol) and 5-chloro 3-pyridinol (13 g, 100 mmol) in DMIF (100 mL) was added powdered K2C03 (13.9 g, 100 mmol). After heating at 60°C for 12 hours, the suspension was poured into water (1 L). The resulting solid was collected by filtration, rinsed with water and dried under vacuum to afford 27.6 g (100%) of the title compound, mp 104-107 °C.

^{1}H NMR (400 MHz) (DMSO-d_6) δ 8.755 (d, J=2.8 Hz, 1H); 8.734 (br s, 1H); 8.576 (br s, 1H); 8.542 (dd, J=9.2, 2.7 Hz, 1H); 7.689 (t, J=2.2 Hz, 1H); 7.122 (d, J= 9.2 Hz, 1H).

EXAMPLE 2

This example illustrates the preparation of 5-amino-2-(3-chloro-5-pyridyloxy)benzonitrile (2.1).



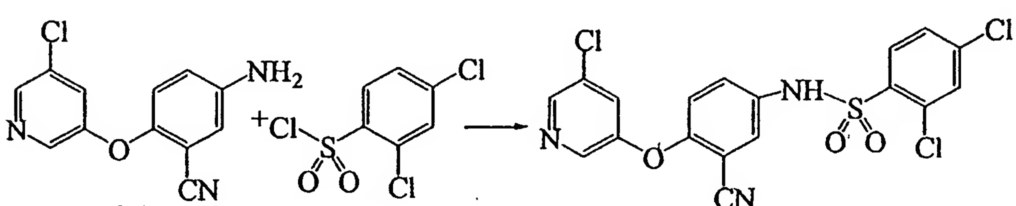
2.1

To a vigorously stirred solution of the intermediate from Example 1 (6.23 g) in ethanol and THF was added a slurry of Raney Nickel (-300 mg, Aldrich). The flask was filled with H_2 at atmospheric pressure and the reduction was monitored by TLC. Starting material disappeared rapidly, to form a nitroso intermediate which gradually was converted to the desired aniline over about 5 hours. Stirring was stopped and Raney Nickel was attracted to the magnetic stirbar. The remaining solution was filtered through Celite® which was then rinsed with ethanol and methylene chloride. The combined organic portions were concentrated to provide 5.75 g of the product aniline as an oil which was used without further purification.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.456 (d, J=1.9 Hz, 1H); 8.3 89 (d, J=2.6 Hz, 1H); 7.38 (m, 1H); 7.03 (m, 3H); 4.06 (m 2H).

EXAMPLE 3

This example illustrates the synthesis of **3.1**.

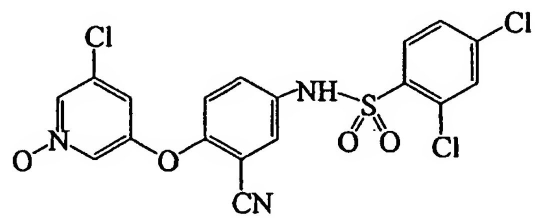


2.1 **3.1**

To a mixture of 5-amino-2-(3-chloro-5-pyridyloxy)benzonitrile from Example 2 (0.457 g) in methylene chloride was added 2,4-dichlorobenzenesulfonyl chloride (0.456 g, from Maybridge), followed by pyridine (150 μL). The reaction progress was monitored by TLC, and upon completion the solvent was removed under vacuum. The resulting residue was partitioned between methylene chloride and water. The organic layer was drawn off and concentrated. The residue was triturated with ether to provide 0.447 g of the title compound as a white solid, mp 154-156 °C.

^1H NMR (400 MHz) ($CDCl_3$) δ 8.59 (s, 1H); 8.42 (s, 1H) 8.08 (d, J=8.5 Hz, 1H); 7.72(t, J=1.8, 1H); 7.605 (d, J=2.7 Hz, 1H) 7.53 (dd, J=8.5, 2 Hz, 1H); 7.48 (dd, J=9.4 Hz, 1H); 7.22 (s, 1H); 7.0 (d, J=9.0 Hz, 1H). m/e (M-H) 456.

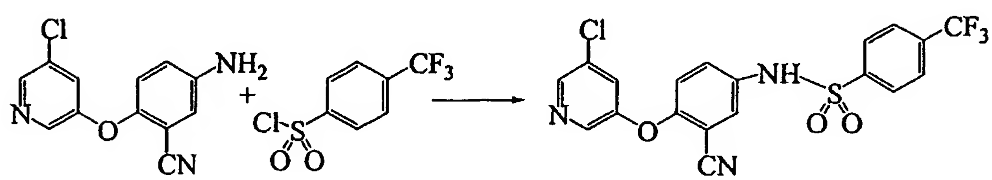
The title compound was oxidized to the corresponding pyridine N-oxide using 3-chloroperoxybenzoic acid in methylene chloride to provide **3.2** as a white solid. m/e 470 (M+H).



3.2

EXAMPLE 4

This example illustrates the synthesis of **4.1**.

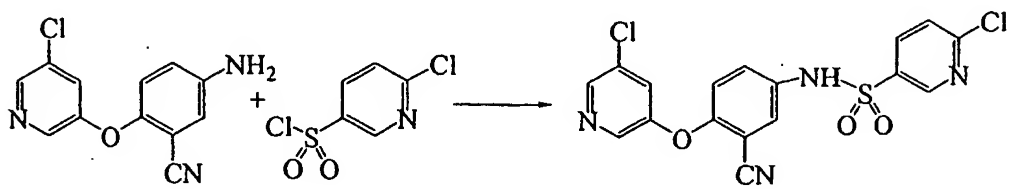


2.1 **4.1**

The title compound was prepared in a manner similar to Example 3, beginning with 1.6 g of the aniline of Example 2 and 1.6 g of 4-(trifluoromethyl)benzenesulfonyl chloride (from Maybridge). The crude product remaining after workup was purified by flash chromatography on silica eluting with 10% ethyl acetate / dichloromethane and then triturated in diethyl ether and collected as a white powder (1.04 g, 35% yield), mp 143-144 °C.

EXAMPLE 5

This example illustrates the synthesis of **5.1**.

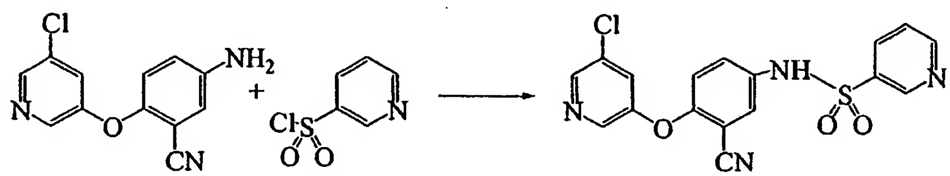


2.1 **5.1**

The title compound was prepared in a manner similar to Example 3, beginning with 397 mg of the aniline prepared as described in Example 2 and 345 mg of 2-chloropyridyl-5-sulfonyl chloride (prepared according to Hoffman, R.V., *Org. Syn. Coll. Vol. VII.*, p. 508-511). The crude product remaining after workup was purified by flash chromatography on silica eluting with 15% ethyl acetate / dichloromethane. The resulting solid was recrystalized from dichloromethane to provide the title compound (270 mg, 40%) as a white solid, m/e 419 (M-H).

EXAMPLE 6

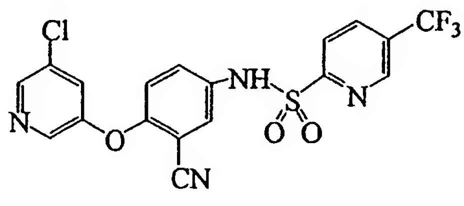
This example illustrates the synthesis of **6.1**.



2.1 **6.1**

The title compound was prepared in a manner similar to Example 3, beginning with 400 mg of the aniline prepared as described in Example 2 and 349 mg of 3-pyridylsulfonyl chloride (prepared using methods similar to those described in *J. Med. Chem.* 40:1149 (1997)). The crude product remaining after workup was purified by flash chromatography on silica eluting with 1% ethanol / dichloromethane. The resulting solid was recrystalized from dichloromethane / diethyl ether and collected as a white solid (121 mg, 19%), mp 161-2 °C.

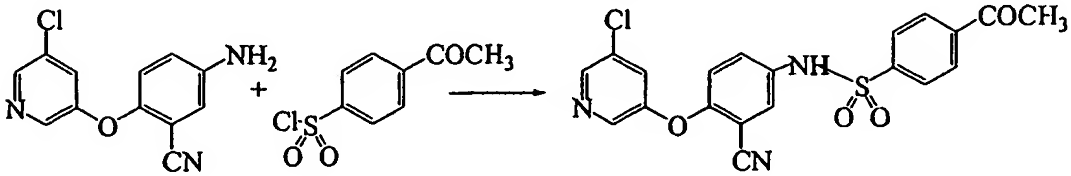
In a similar manner, **6.2** was prepared from aniline **2.1** and 5-trifluoromethyl-2-pyridinesulfonyl chloride, mp 174-176 °C.



6.2

EXAMPLE 7

This example illustrates the preparation of **7.1**.



2.1 **7.1**

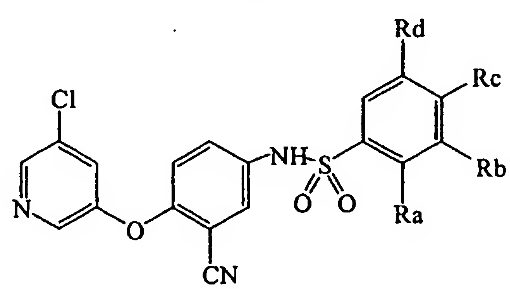
A round-bottomed flask was charged with the aniline prepared according to Example 2 (229 mg, 0.94 minol), 4-acetylbenzenesulfonyl chloride (205 mg, 0.94 mmol, prepared according to Hoffman, R.V., Org. Syn. Coll. Vol. VII, p. 508-511), pyridine (75 mg, 0.94 mmol, Aldrich Chemical Co.), and a catalytic amount of DMAP (Aldrich Chemical Co.). Five mL of dichloromethane were added and the reaction was stirred at room temperature for eight hours. The reaction was then diluted with 25 mL of dichloromethane and washed successively with 10 mL of 1N HCl and brine. The organic portion was dried over $MgSO_4$ and passed through a plug of silica gel to remove baseline impurities. The resulting solid was triturated in hexanes to provide 362 mg (90%) of the title compound as a white solid.

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.81 (1H, s); 8.52 (1H, d, J=1.8 Hz); 8.43 (1H, d, J=2.3 Hz); 8.11 (2H, dd, J=6.8 Hz, 2.0 Hz); 7.90 (2H, dd, J=6.8 Hz, 2.0 Hz); 7.85 (1H, dd, J=4 .4 Hz, 2.2 Hz); 7.53 (1H, d, J=2.7 Hz); 7.35 (1H, dd, J=9.1 Hz, 2.8 Hz); 7.35 (1H, d, J=9.1 Hz); 2.61 (3H, s).

MS ESI m/e: 425.8 (M - H).

The compounds provided in Table 1 were prepared using the methods described in Examples 1-7.

Table 1

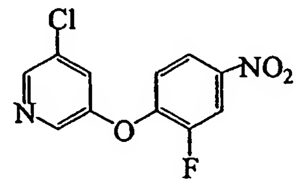


	Ra	Rb	Rc	Rd	mp (°C)
7.2	Cl	H	Cl	CH_3	181-182

7.3	H	H	OCF_3	H	118-120
7.4	H	H	CN	H	160-163
7.5	H	H	SO_2CH_3	H	174-175

EXAMPLE 8

This example illustrates the preparation of 3-fluoro-4-(3-chloro-5-pyridyloxy)nitrobenzene (**8.1**).



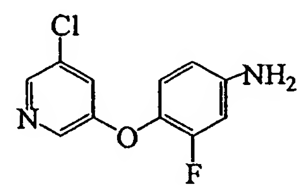
8.1

3,4-Difluoronitrobenzene (5.0 g, 32 mmol) and 5-chloro-3-pyridinol were combined using the procedure described in Example 1, to produce 8.2 g of the title compound.

^{1}H NMR (400 MHz) (DMSO-d_6) δ 8.562 (d, *J*=1.9 Hz, 1H); 8.537 (d, *J*=2.5 Hz, 1H); 8.384 (dd, *J*=10.8, 2.8 Hz, 1H); 8.117 (ddd, *J*=9.1, 2.7, 1.5 Hz, 1H); 7.967 (t, *J*=2.2 Hz, 1H); 7.418 (dd, *J*= 9.2, 8.4 Hz, 1H).

EXAMPLE 9

This example illustrates the preparation of 3-fluoro-4-(3-chloro-5-pyridyloxy)aniline (**9.1**).



9.1

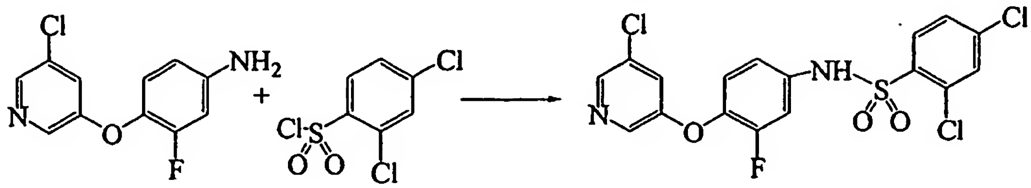
Using the method of Example 2, 3-fluoro-4-(3-chloro-5-pyridyloxy)nitrobenzene (**8.1**, 8.0 g) was converted to the title compound which was used directly in subsequent reactions.

MS (M + H) 239.1.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.242 (br s, 2H); 7.142 (d, *J*=2.2 Hz, 1H); 6.937 (t, *J*=8.7 Hz, 1H); 6.5 12 (dd, *J*=12, 2.6 Hz, 1H); 6.444 (ddd, *J*=8.4, 2.7, 1.4 Hz, 1H); 3.62 (br s, 2H).

EXAMPLE 10

This example illustrates the preparation of **10.1**.

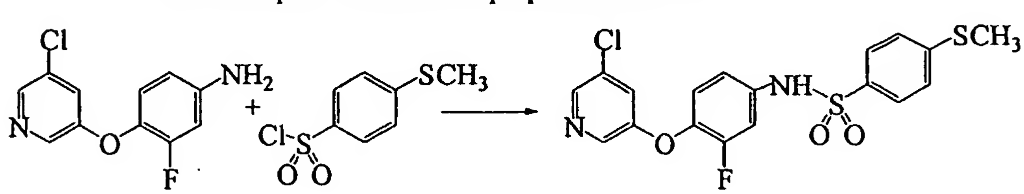


9.1 **10.1**

3-Fluoro-4-(3-chloro-5-pyridyloxy)aniline (239 mg, see Example 9) and 2,4-dichlorobenzenesulfonyl chloride (416 mg, Maybridge), were combined in a similar manner to that described in Example 3. The crude product was purified by flash chromatography on silica, eluting with 5% ethyl acetate / dichloromethane. The product fractions were concentrated and the solid was recrystallized from diethyl ether / hexanes to provide the title compound as a white solid (350 mg, 45%), mp 149-151 °C.

EXAMPLE 11

This example illustrates the preparation of **11.1**.



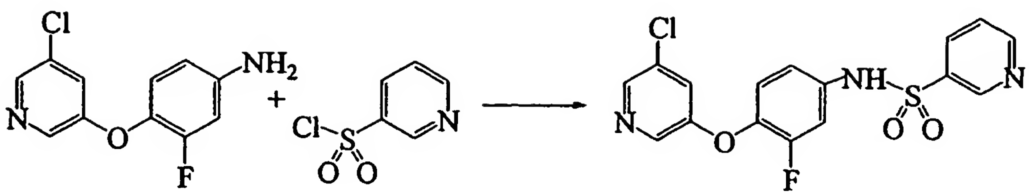
9.1 **11.1**

3-Fluoro-4-(3-chloro-5-pyridyloxy)aniline (310 mg, see Example 9) and 4-methylthiobenzenesulfonyl chloride (298 mg, prepared as described in Burton, *et al., J. Chem. Soc.*, 604-5 (1948)), were combined in a manner similar to that described in Example 3. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate / hexanes / dichloromethane (1:5:4). The product fractions were concentrated and the solid was recrystallized from hexanes / diethyl ether to provide the title compound as a white solid (315 mg, 57%), mp 130-131 °C.

The title compound was oxidized with mCPBA to the corresponding sulfoxide (**11.2**, mp 140-144 °C). The corresponding sulfone (**11.3**) was prepared using 4-(methylsulfonyl)benzenesulfonyl chloride (mp 165-168 °C).

EXAMPLE 12

This example illustrates the preparation of **12.1**.

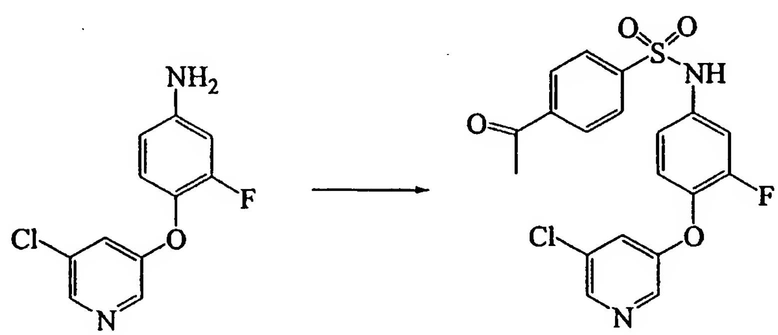


9.1 12.1

The title compound was prepared in a manner similar to Example 3, beginning with 3-pyridylsulfonyl chloride (335 mg, see Example 6) and 3-fluoro-4-(3-chloro-5-pyridyloxy)aniline (310 mg, see Example 9) with the addition of a catalytic amount of 4-dimethylaminopyridine. When reaction was complete by TLC, the mixture was filtered to remove amine salts. The filtrate was concentrated and the residue was purified by flash chromatography on silica, eluting with 5% methanol / dichloromethane. The product fractions were combined, concentrated, and the residue was triturated with diethyl ether to provide the title compound as a white solid (221 mg, 32%), mp 129 °C.

EXAMPLE 13

This illustrates the synthesis of 5-(4-acetylbenzenesulfonamido-2-fluorophenoxy)-3-chloropyridine (13.1).



9.1 13.1

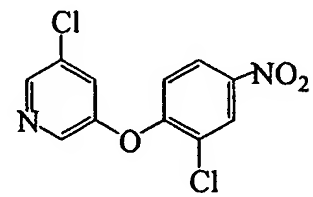
This was prepared using methods outlined in Examples 10-12, starting with 238 mg (1.0 mmol) of aniline **9.1**, 218 mg (1.0 mmol) of 4-acetylbenzenesulfonyl chloride, 79 mg (1.0 mmol) of pyridine, catalytic DMAP, and S mL of methylene chloride. The title compound was obtained as a white solid (269 mg, 64%).

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.75 (1H, d, J=4.7 Hz); 8.38 (1H, dd, J_1=4.8 Hz J_2=2.1 Hz); 8.26 (1H, dd, J_1=5.0 Hz J_2=2.4 Hz) 8.09 (2H, m); 7.91 (2H, m); 7.52 (1H, dd, J_1=4.7 Hz J_2=2.6 Hz); 7.21 (1H, dt, J_1=5 Hz J_2=1.0 Hz); 7.12 (1H, dd,

J_1=12.2 Hz J_2=1 .0 Hz); 6.92 (1H, d, J=8.8 Hz); 2.59 (3H, t, J=2.1 Hz). MS ESI m/e: 418.7 (M - H).

EXAMPLE 14

This example illustrates the synthesis of 3-chloro-4-(3-chloro-5-pyridyloxy)nitrobenzene (**14.1**).



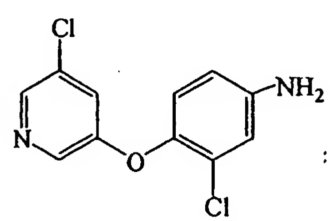
14.1

3-Chloro-4-fluoronitrobenzene (5.0 g, 28 mmol) and 5-chloro-3-pyridinol were combined using the procedure described in Example 1, to produce 7.9 g of the title compound.

^{1}H NMR (400 MHz) (DMSO-d_6) δ 8.571 (d, J=2.0 Hz, 1H); 8.509 (d, J=2.4 Hz, 1H); 8.499 (d, J=2.7 Hz, 1H); 8.208 (dd, J=9.0, 2.7 Hz, 1H); 7.949 (t, J=2.3 Hz, 1H); 7.335 (d, J= 9.1 Hz, 1H).

EXAMPLE 15

This example illustrates the preparation of 3-chloro-4-(3-chloro-5-pyridyloxy)aniline (**15.1**).



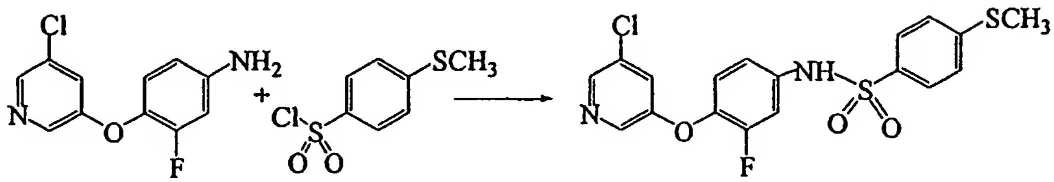
15.1

Using the method of Example 2, 3-chloro-4-(3-chloro-5-pyridyloxy)nitrobenzene (7.6 g) was converted to the title compound (7.2 g) and which was used directly in subsequent reactions.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.244 (br s, 1H); 8.211 (br s, 1H); 7.096 (br 5, 1H); 6.929 (d, J=8.6 Hz, 1H); 6.785 (d, J=2.6 Hz, 1H); 6.592 (dd, J=8.6, 2.6 Hz, 1H); 3.577 (br s, 2H). MS (M + H) 255.1.

EXAMPLE 16

This example illustrates the preparation of **16.1**.

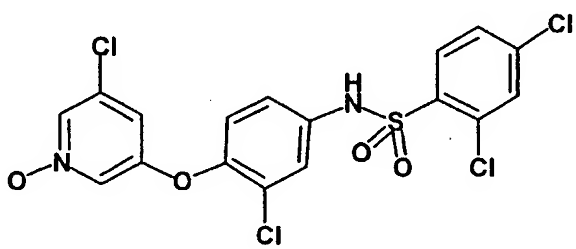


9.1 **16.1**

3-Chloro-4-(3-chloro-5-pyridyloxy)aniline (410 mg, **15.1**) and 2,4-dichlorobenzenesulfonyl chloride (390 mg, Maybridge), were combined in a similar manner to that described in Example 3. The crude product was purified by flash chromatography on silica, eluting with 5% ethyl acetate / dichloromethane. The product fractions were concentrated and the residue was triturated in hexanes to provide the title compound as a white solid (538 mg, 73%), mp 128-130 °C.

^{1}H NMR (400 MHz) (DMSO) δ 8.40 (d, *J*=1.8 Hz, 1H); 8.24 (d, *J*=2.4 Hz, 1H); 8.06 (d, *J*=8.5 Hz, 1H); 7.90 (d, *J*=2.0 Hz, 1H); 7.65 (dd, *J*=2, 8.5 Hz, 1H); 7.48 (t, *J*=2.2, 1H); 7.28 (d, *J*=2.5 Hz, 1H); 7.21 (d, *J*=8.84 Hz, 1H); 7.10 (dd, *J*=2.5, 7.1, 1H). MS m/e 465 (M+1).

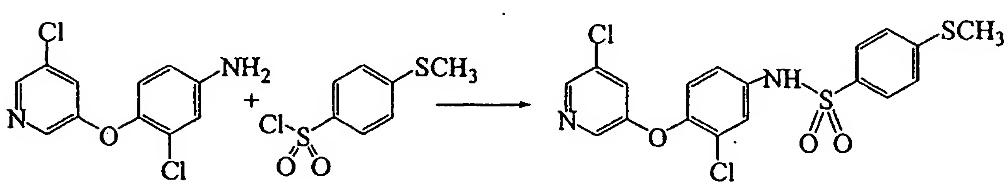
Compound 16.1 was oxidized with 3-chloroperoxybenzoic acid to produce the corresponding pyridine N-oxide, 16.2, as a white solid after trituration in diethyl ether, mp 205-207 °C.



16.2

EXAMPLE 17

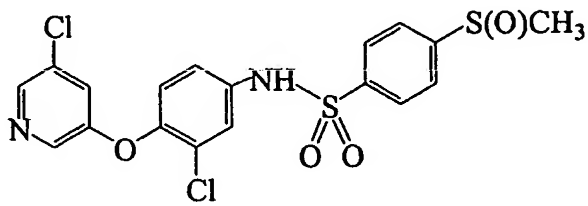
This example illustrates the preparation of **17.1**.



15.1 **17.1**

3-Chloro-4-(3-chloro-5-pyridyloxy)aniline (309 mg, 15.1) and 4-methylthiobenzenesulfonyl chloride (223 mg, prepared as described in Burton, *et al.*, *J. Chem. Soc.*, 604-5 (1948)), were combined in a manner similar to that described in Example 3. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate / hexanes / dichloromethane (1:5:4). The product fractions were concentrated and the residue obtained was triturated in hexanes to provide the title compound as a white solid (200 mg, 37%), mp 96-98 °C.

Oxidation of **17.1** *to sulfoxide* **17.2**

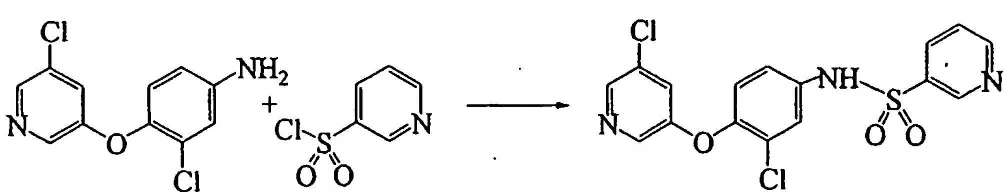


17.2

Compound **17.1** was oxidized to the corresponding sulfoxide using Oxidation to sulfoxide potassium peroxymonosulfate in methanol and acetone. The reaction was monitored by TLC. After the reaction was complete, the mixture was filtered and the filtrate was washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica, eluting with 50% to 100% ethyl acetate / dichloromethane. Solvent was removed from the product fractions, and the residue was triturated in hexanes. The white solid product was collected by filtration to provide 121 mg of **17.2** (63%), mp 127-128 °C.

EXAMPLE 18

This example illustrates the preparation of **18.1**.

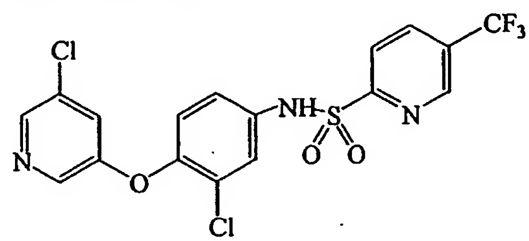


15.1 **18.1**

The title compound was prepared in a manner similar to Example 3, beginning with 3-pyridylsulfonyl chloride (335 mg, see Example 6) and 3-chloro-4-(3-

chloro-5-pyridyloxy)aniline (411 mg, **15.1**) with the addition of a catalytic amount of 4-dimethylaminopyridine. When the reaction was completed by TLC, the mixture was filtered to remove amine salts. The filtrate was concentrated and the residue was purified by flash chromatography on silica, eluting with 5% methanol / dichloromethane. The product fractions were combined, concentrated, and the residue was triturated dichloromethane to provide the title compound as a white solid (149 mg, 22%), mp 164-165 °C.

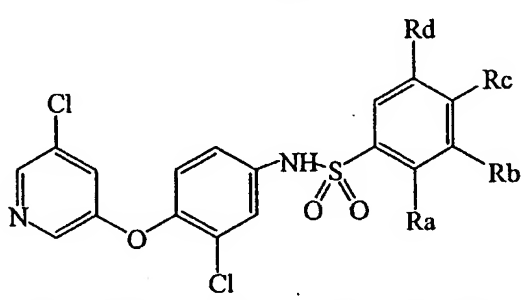
In a similar manner, **18.2** (mp 174- 175 °C) was prepared from aniline **15.1** and 5-trifluoromethyl-2-pyridinesulfonyl chloride.



18.2

The compounds provided in Table 2 were prepared using commercially available intermediates and/or using the intermediates and methods described in the examples above.

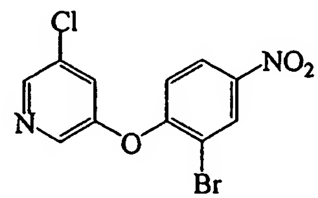
Table 2



	Ra	Rb	Rc	Rd	mp (°C) or m/e
18.3	H	H	CF_3	H	172-174°C
18.4	Cl	H	CF_3	H	111-113°C
18.5	H	H	$COCH_3$	H	434.7
18.6	H	Cl	Cl	H	460.9

EXAMPLE 19

This example illustrates the preparation of 3-bromo-4-(3-chloro-5-pyridyloxy)nitrobenzene (**19.1**).



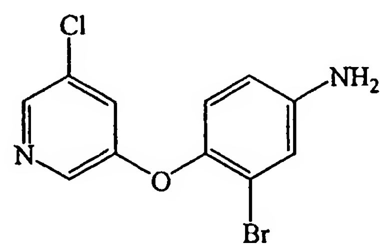
19.1

3-Bromo-4-fluoronitrobenzene (available from Reidel) and 5-chloro-3-pyridinol were combined using the procedure described in Example 1, to produce the title compound.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.61 (d, J = 2.6 Hz, 1H), 8.57 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), 8.24 (dd, J = 9.3, 2.6 Hz, 1H), 7.94 (dd, J = 2.4, 2.2 Hz, 1H), 7.3 (d, J = 9.0 Hz, 2H). MS (EI): *m/z* 333 (25, M+H), 332 (15, M+H), 331 (100, M+H), 330 (10, M+H), 329 (76, M+H).

EXAMPLE 20

This example illustrates the preparation of 3-bromo-4-(3-chloro-5-pyridyloxy)aniline (**20.1**).



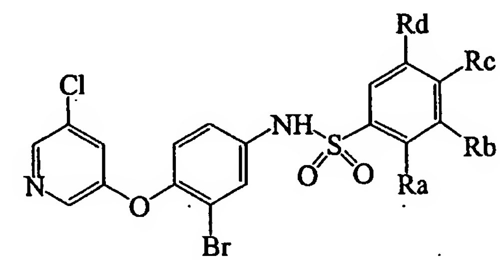
20.1

Using the method of Example 2, 3-bromo-4-(3-chloro-5-pyridyloxy)nitrobenzene (**19.1**) was converted to the title compound which was used directly in subsequent reactions.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.32 (d, J = 2.1 Hz, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.28 (dd, J = 2.4, 2 Hz, 1H), 7.2 (d, J = 8.7 Hz, 1H), 6.9 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 8.7, 2.6 Hz, 1H). MS (EI): *m/e* 304 (5, M+H), 303 (35, M+H), 302 (20, M+H), 301 (100, M+H), 300 (15, M+H), 299 (90, M+H).

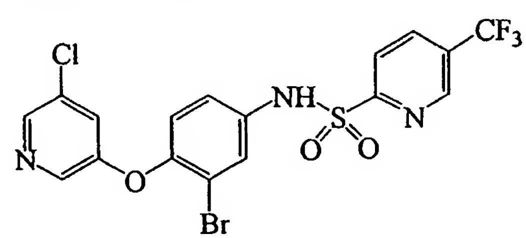
The compounds provided in Table 3 were prepared using **20.1** and commercially available intermediates and/or using the intermediates and methods described in the examples above.

Table 3



	Ra	Rb	Rc	Rd	mp (°C)
20.2	Cl	H	Cl	H	114-115
20.3	H	H	SCH_3	H	160-162
20.4	H	H	$S(O)CH_3$	H	169-171

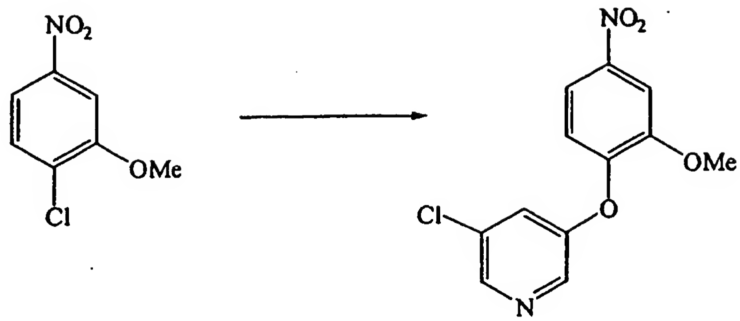
Similarly, **20.5** was prepared from aniline **20.1** and 5-trifluoromethyl-2-pyridinesulfonyl chloride, mp 202-204 °C.



20.5

EXAMPLE 21

This example illustrates the preparation of 5-(4-nitro-2-methoxyphenoxy)-3-chloropyridine (**21.1**).

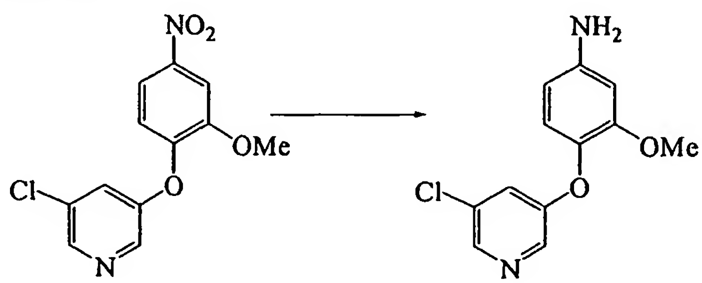


21.1

A round-bottomed flask was charged with 2-chloro-5-nitroanisole (1.03 g, 5.49 mmol, Avocado Chemical Co.), 5-chloro-3-pyridinol (750 mg, 5.76 mmol, Aldrich Chemical Co.), cesium carbonate (1.97 g, 6.04 mmol, Aldrich Chemical Co.), and anhydrous DMF (16 mL). The mixture was heated at 100 °C for 18 hours. The temperature was then increased to 130°C for an additional two hours, after which the reaction was allowed to cool to room temperature. The reaction mixture was poured into 800 mL of distilled water, and extracted three times with 300 mL ethyl acetate. The combined extracts were dried over $MgSO_4$ and filtered. Solvent was removed from the filtrate under vacuum and the crude product was purified by flash chromatography on silica gel (5% hexanes in CH_2Cl_2 as eluant) to provide the title compound (1.42 g, 93%) as a yellow solid. MS ESI m/e: 281.1 (M + H).

EXAMPLE 22

This example illustrates the synthesis of 5-(4-amino-2-methoxyphenoxy)-3-chloropyridine (**22.1**).



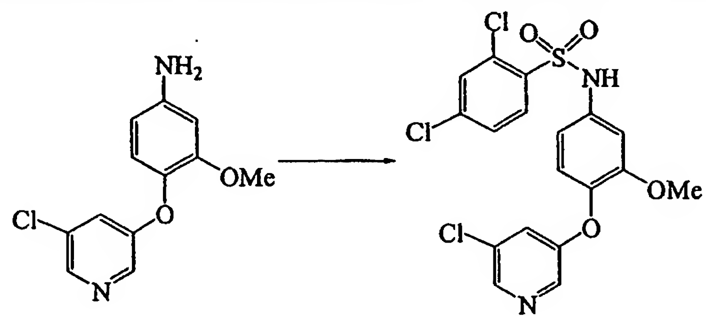
21.1 **22.1**

Using the method of Example 2, the nitro compound prepared in Example 21 (1.54 g, 6.56 mmol) was converted to 1.38 g (99%) of the title compound as an off-white solid. The product was used without further purification (upon standing several

days in air the compound developed a very dark brown color). MS ESI m/e: 251.1 (M + H).

EXAMPLE 23

This example illustrates the synthesis of 5-(4-(2,4-dichlorobenzenesulfonamido)-2-methoxyphenoxy)-3-chloropyridine (**23.1**).



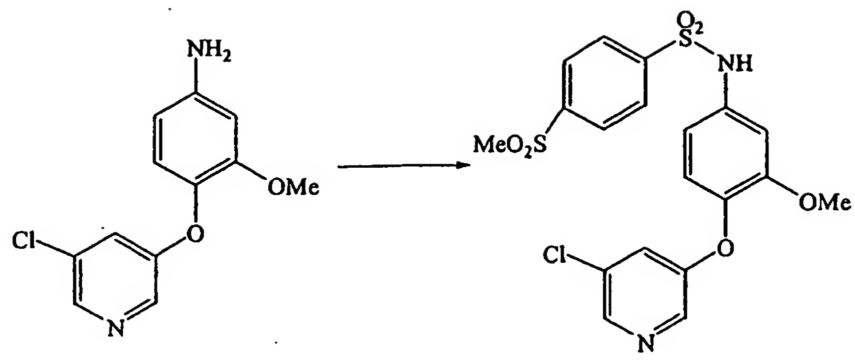
22.1 **23.1**

A round-bottomed flask was charged with aniline 22.1 (96 mg, 0.39 mmol), 2,4-dichlorobenzenesulfonyl chloride (104 mg, 0.42 mmol, Maybridge Chemical Co.), pyridine (28 mg, 0.39 mmol, Aldrich Chemical Co.), and a catalytic amount of DMAP (Aldrich Chemical Co.). Three mL of dichloromethane was added and the reaction mixture was stirred at room temperature for eight hours. The resulting mixture was then diluted with 15 mL of dichloromethane and washed successively with 10 mL of 1N HCl and brine. The combined organic portions were dried over $MgSO_4$ then passed through a plug of silica gel to remove baseline impurities. Solvent was removed from the filtrate and the resulting solid was triturated in hexanes to provide the title compound (69 mg, 40%) as a white powder.

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.81 (1H, s); 8.29 (1H, d, J=2.1 Hz); 8.11 (1H, d, J=2.4 Hz); 8.07 (1H, d, J=8.5 Hz); 7.88 (1H, d, J=2.0 Hz); 7.63 (1H, dd, J=8.7 Hz, 2.1 Hz); 7.20 (1H, dd, J=4 .4 Hz, 2.1 Hz); 7.07 (1H, d, J=8.7 Hz); 6.91 (1H, d, J= 2.4 Hz); 6.68 (1H, dd, J=8.7 Hz, 2.5 Hz); 3.65 (3H, s). MS ESI m/e: 459.0 (M + H).

EXAMPLE 24

This example illustrates the synthesis of 5-(4-methylsulfonylbenzenesulfonamido-2-methoxyphenoxy)-3-chloropyridine (**24.1**).



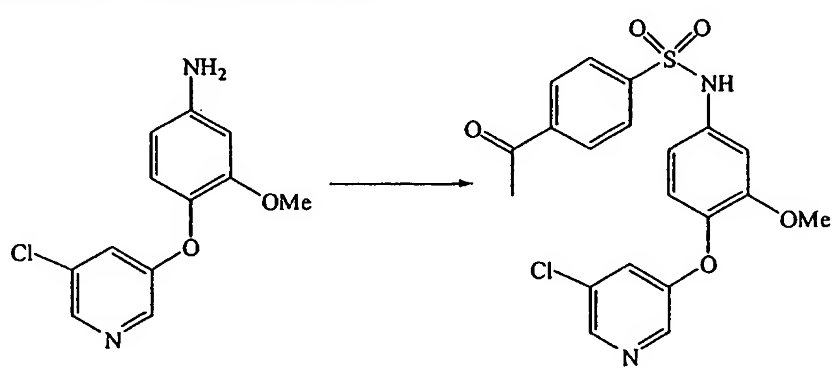
22.1 24.1

The title compound was prepared using the general procedure described in Example 22, starting with 150 mg (0.61 mmol) of the aniline, 155 mg (0.61 mmol, Aldrich Chemical Co.) of 4-methylsulfonebenzenesulfonyl chloride, 48 mg (0.61 mmol) of pyridine, catalytic DMAP, and 5 mL of methylene chloride. Following workup, the title compound was obtained (67 mg, 24%) as a white solid.

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.63 (1H, s); 8.30 (1H, d, J=2.0 Hz); 8.14 (2H, m); 8.04 (1H, dd, J=8.6 Hz, 1.9 Hz); 7.27 (1H, dd, J=4.5 Hz, 2.2 Hz); 7.08 (1H, d, J=8.6 Hz); 6.93 (1H, d, J=2.4 Hz); 6.70 (1H, dd, J=8.6 Hz, 2.4 Hz); 3.67 (3H s); 3.28 (3H, s). MS ESI m/e: 467.0 (M - H).

EXAMPLE 25

This example illustrates the synthesis of 5-(4-acetylbenzenesulfonamido-2-methoxyphenoxy)-3-chloropyridine (**25.1**).



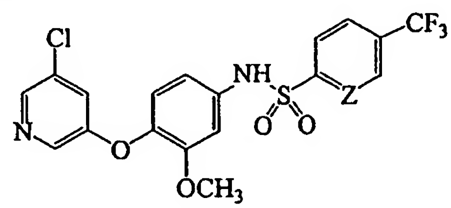
22.1 25.1

The title compound was prepared using the procedure described in Example 7, starting with 82 mg (0.33 mmol) of aniline **22.1**, 72 mg (0.33 mmol) of 4-acetylbenzenesulfonyl chloride, 26 mg (0.33 mmol) of pyridine, catalytic DMAP, and 2

mL of methylene chloride. The title compound was produced (92 mg, 65%) as a white solid.

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.52 (1H, s); 8.29 (1H, d, J=1.9 Hz); 8.10 (3H, m); 7.92 (2H, dd, J=8.0 Hz, 2.3 Hz); 7.23 (1H, dd, J=4.5 Hz, 2.4 Hz); 7.06 (1H, d, J=8.6 Hz); 6.93 (1H, dd, J=8.6 Hz, 2.4 Hz); 6.70 (1H, dd, J=8.6 Hz, 2.4 Hz); 3.65 (3H, s); 2.60 (3H, s). MS ESI m/e: 431.1 (M - H).

In a similar manner, **25.2** and **25.3** were prepared from aniline **22.1** and the appropriate sulfonyl chloride.

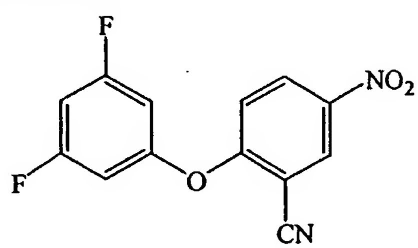


25.2 Z = N

25.3 Z = CH

EXAMPLE 26

This example illustrates the preparation of 5-nitro-2-(3,5-difluorophenoxy)-benzonitrile (**26.1**).

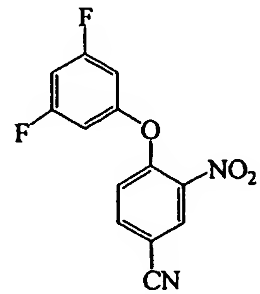


26.1

2-Chloro-5-nitrobenzonitrile (4.6 g, 25 mmol) and 3,5-difluorophenol were combined using the procedure described in Example 1, to produce 6.6 g of the title compound.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.598 (d, J=2.8 Hz, 1H); 8.396 (ddd, J=9.3, 2.8, 1.2 Hz, 1H); 7.259 (d, J=0.8 Hz, 1H); 7.044 (d, J=9.6 Hz, 1H); 6.821 (m, 1H); 6.722 (m, 2H).

In a similar manner, 4-chloro-3-nitrobenzonitrile (4.6 g, 25 mmol) and 3,5-difluorophenol were combined to produce 6.9 g of 3-nitro-4-(3,5-difluorophenoxy)-benzonitrile (**26.2**), mp 132-136 °C.

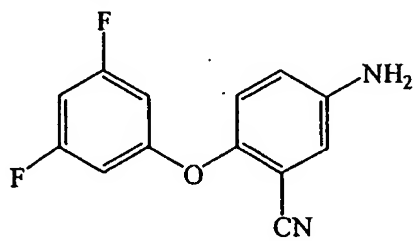


26.2

^{1}H NMR (400 MHz) (DMSO-d_6) δ 8.72 (d, J=2.0 Hz, 1H); 8.165 (dd, J=8.8, 1.9 Hz, 1H); 7.422 (d, J=8.8 Hz, 1H); 7.227 (m, 1H); 7.103 (m, 2H).

EXAMPLE 27

This example illustrates the preparation of 5-amino-2-(3,5-difluorophenoxy)benzonitrile (**27.1**).

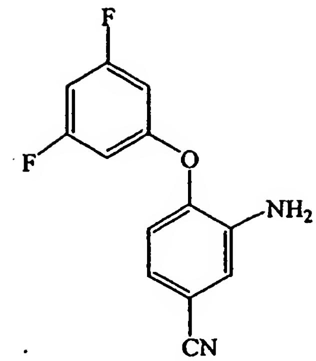


27.1

Using the method of Example 2, 5-nitro-2-(3,5-difluorophenoxy)-benzonitrile (**26.1**, 6.6 g) was converted to the title compound (5.47 g, mp 80-84°C) which was used directly in subsequent reactions.

^{1}H NMR (400 MHz) (TFA/DMSO-d_6) δ 11.2 (br s, 2H); 7.083 (d, J=9.2 Hz, 1H); 7.077 (d, J=2.8 Hz, 1H); 7.033 (dd, J=9.2, 2.4 Hz, 1H); 6.998 (tt, J=9.2, 2.4 Hz, 1H); 6.727 (dd, J=8.4, 2.0 Hz, 2H).

Similarly, 3-amino-4-(3,5-difluorophenoxy)benzonitrile (**27.2**) was prepared from **26.2**.

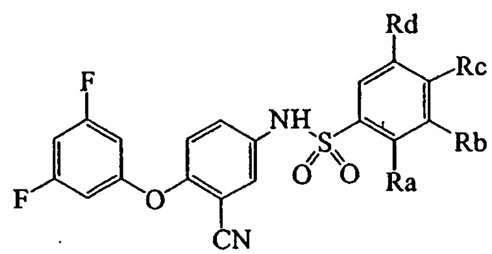


27.2

^{1}H NMR (400 MHz) (DMSO-d_6) δ 7.14 (d, J=2.0 Hz, 1H); 7.03-6.96 (m, 3H); 6.70 (dd, J=8.6, 2.3 Hz, 2H); 5.60 (s, 2H).

The compounds provided in Table 4 were prepared using **27.1** and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

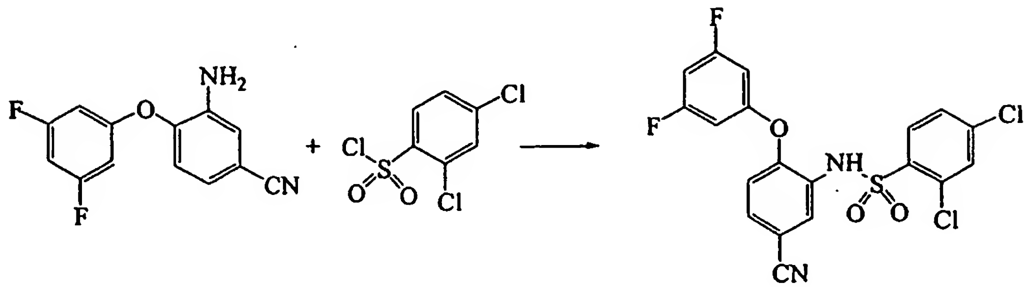
Table 4



	Ra	Rb	Rc	Rd	mp(°C)or m/e
27.3	Cl	H	Cl	H	452.7
27.4	H	H	OCH_3	H	414.8
27.5	H	H	I	H	510.6
27.6	H	H	$C(O)CH_3$	H	482.7
27.7	H	H	CF_3	H	141-144 °C

EXAMPLE 28

This example illustrates the preparation of **28.1**.

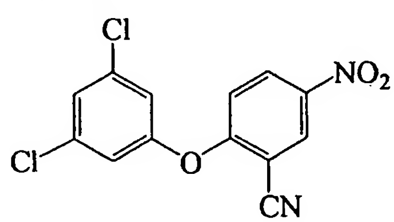


28.1

3-Amino-4-(3,5-difluorophenoxy)benzonitrile (201 mg, **27.2**) and 2,4-dichlorobenzenesulfonyl chloride (302 mg, Maybridge), were combined in a similar manner to that described in Example 3, then heated to 40 °C. The crude product obtained after workup was purified by flash chromatography on silica, eluting with dichloromethane. The product fractions were concentrated and the residue was triturated with diethyl ether to provide the title compound as a white solid (150 mg, 37%), mp 197-200 °C.

EXAMPLE 29

This example illustrates the preparation of 5-nitro-2-(3 ,5-dichlorophenoxy)-benzonitrile (**29.1**).



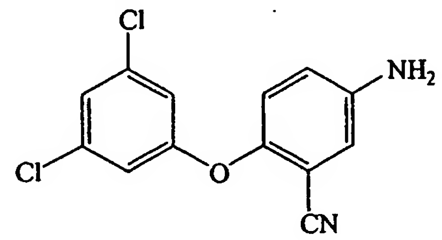
29.1

2-Chloro-5-nitrobenzonitrile (0.9 g, 5 mmol) and 3,5-dichlorophenol were combined using the procedure described in Example 1, to produce 1.5 g of the title compound, mp 188-190 °C.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.597 (d, J=2.4 Hz, 1H); 8.397 (ddd, J=9.2, 2.8, 0.8 Hz, 1H); 7.360 (dd, J=3.2, 2.0 Hz, 1H); 7.089 (dd, J=1.6, 0.8 Hz, 2H) 7.008 (d, J=9.6 Hz, 1H).

EXAMPLE 30

This example illustrates the preparation of 5-amino-2-(3,5-dichlorophenoxy)benzonitrile (**30.1**).

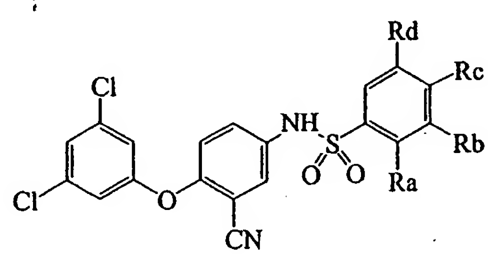


30.1

To a solution of 5-nitro-2-(3,5-dichlorophenoxy)benzonitrile (**29.1**, 1.5 g) in ethyl acetate (45 mL) was added stannous chloride dihydrate (5.47 g). The mixture was heated to 85°C for 30 minutes during which time a thick white precipitate formed. The reaction vessel was cooled and the mixture was treated with 100 mL of 0.5 N NaOH. The resulting mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford the title compound which was used without further purification. MS m/e 279 (M+H).

The compounds provided in Table 5 were prepared using **30.1** and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

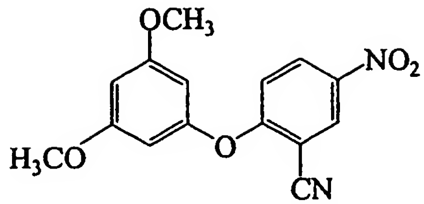
Table 5



	Ra	Rb	Rc	Rd	mp (°C)
30.2	Cl	H	Cl	H	143-144
30.3	H	H	CF_3	H	148-149

EXAMPLE 31

This example illustrates the preparation of 5-nitro-2-(3,5-dimethoxyphenoxy)benzonitrile (**31.1**).



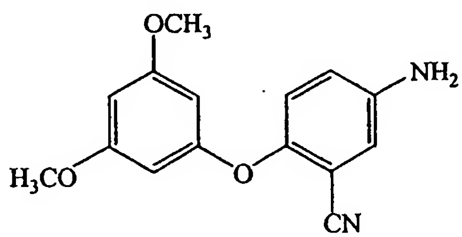
31.1

2-Chloro-5-nitrobenzonitrile (5.3 g) and 3,5-dimethoxyphenol (4.5 g, Aldrich) were combined using the procedure described in Example 1, to produce the title compound as a brown solid.

^{1}H NMR (400 MHz) (DMSO) δ 8.84 (d, *J*=2.8, 1H); 8.44 (dd, *J*=9.3, 2.8 Hz, 1H); 7.07 (d, *J*=9.3 Hz, 1H); 6.51 (s, 3H); 3.76 (s, 6H).

EXAMPLE 32

This example illustrates the preparation of 5-amino-2-(3,5-dimethoxyphenoxy)benzonitrile (**32.1**).



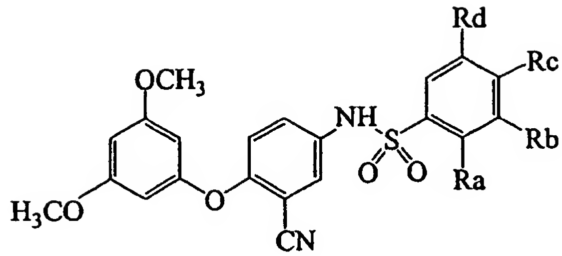
32.1

To a solution of 5-nitro-2-(3,5-dichlorophenoxy)benzonitrile (**31.1**, 8.76 g) in ethyl acetate was added tin chloride (33 g). The mixture was heated to reflux for one hour. The resulting mixture was cooled and 0.5 N sodium hydroxide solution was added to induce the precipitation of tin salts which were removed by filtration. The filtrate was concentrated to provide 7.5 g of the title compound as an orange solid which was used in subsequent reactions without purification.

^{1}H NMR (400 MHz) (DMSO-d_6) δ 6.95-6.87 (m, 3H); 6.25 (t, *J*=2.2 Hz, 1H); 6.04 (d, *J*=2.2 Hz, 2H); 5.49 (s, 2H); 3.70 (s, 6H).

The compounds provided in Table 6 were prepared using **32.1** and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

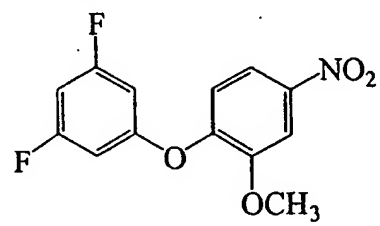
Table 6



	Ra	Rb	Rc	Rd	mp (°C) or m/e
32.2	Cl	H	Cl	H	477
32.3	Cl	H	CF_3	H	101-105°C
32.4	H	H	I	H	439
32.5	H	H	OCH_3	H	162-164°C

EXAMPLE 33

This example illustrates the preparation of 3-methoxy-4-(3,5-difluorophenoxy)-nitrobenzene (33.1).

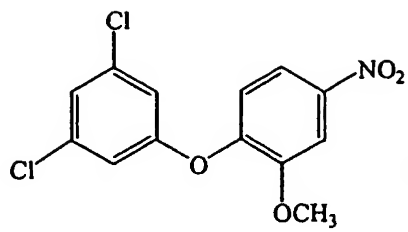


33.1

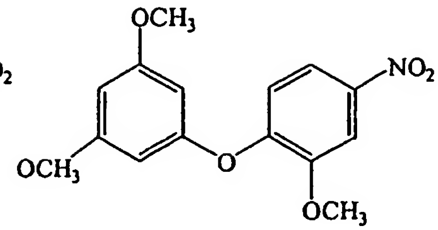
4-Chloro-3-methoxynitrobenzene (2.64 g) and 3,5-difluorophenol (Aldrich) were combined using the procedure described in Example 1 and heated to 125°C, to produce the title compound as a thick brown oil which solidified on trituration with hexane/methanol to yield 1.33 g of **33.1** as a red solid.

^{1}H NMR (400 MHz) (DMSO-d_6) δ 7.963 (d, J=2.6 Hz, 1H); 7.903 (dd, J=8.8, 2.7 Hz, 1H); 7.3 16 (d, J=8.8 Hz, 1H); 7.035 (m, 1H); 6.796 (m, 2H); 3.909 (s, 3H).

In a similar manner, 3-methoxy-4-(3,5-dichlorophenoxy)nitrobenzene (33.2) and 3-methoxy-4-(3,5-dimethoxyphenoxy)nitrobenzene (33.3) were prepared beginning with 3,5-dichlorophenol and 3,5-dimethoxyphenol, respectively.



33.2



33.3

33.2 3-methoxy-4-(3,5-dichlorophenoxy)nitrobenzene

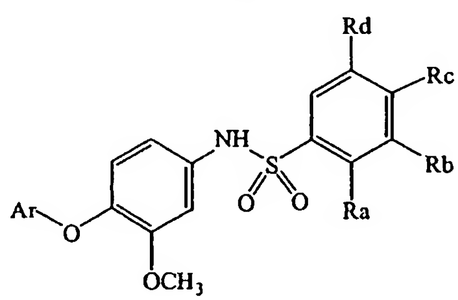
^{1}H NMR (400 MHz) (DMSO-d_6) δ 7.960 (d, J=2.6 Hz, 1H); 7.900 (dd, J=8.9, 2.7 Hz, 1H); 7.394 (t, J=1.7 Hz, 1H); 7.3 10 (d, J=8.8 Hz, 1H); 7.107 (t, J=1.4 Hz, 2H); 3.907 (s, 3H).

33.3 3-methoxy-4-(3,5-dimethoxyphenoxy)nitrobenzene

^{1}H NMR (400 MHz) (DMSO-d_6) δ 7.910 (d, J=2.6 Hz, 1H); 7.862 (dd, J=8.8, 2.6 Hz, 1H); 7.064 (d, J=8.8 Hz, 1H); 6.353 (t, J=2.2 Hz, 1H); 6.207 (d, J=2.2 Hz, 2H); 3.927(s, 3H); 3.716 (s, 6H).

Each of the nitrobenzene derivatives (**33.1, 33.2 and 33.3**) were reduced to the corresponding aniline derivative using the Raney nickel procedure of Example 2. The aniline derivatives were then converted to the compounds shown in Table 7 using commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

Table 7

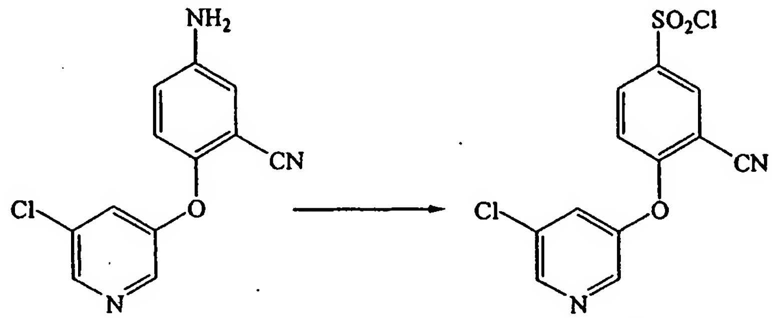


	Ar	Ra	Rb	Rc	Rd	mp(°C)
33.4	3,5-dichlorophenyl	Cl	H	Cl	H	128-131
33.5	3,5-difluorophenyl	H	H	CF_3	H	141-143
33.6	3,5-dichlorophenyl	H	H	CF_3	H	165-166
33.7	3,5-difluorophenyl	Cl	H	Cl	H	120-124
33.8	3,5-difluorophenyl	H	H	OCH_3	H	129-133

	Ar	Ra	Rb	Rc	Rd	mp(°C)
33.9	3,5-dimethoxyphenyl	Cl	H	Cl	H	100-103
33.10	3,5-dimethoxyphenyl	Cl	H	CF_3	H	72-79
33.11	3,5-dimethoxyphenyl	H	H	OCH_3	H	92-95

EXAMPLE 34

This example illustrates the synthesis of 5-(4-chlorosulfonyl-2-cyanophenoxy)-3-chloropyridine (**34.1**).

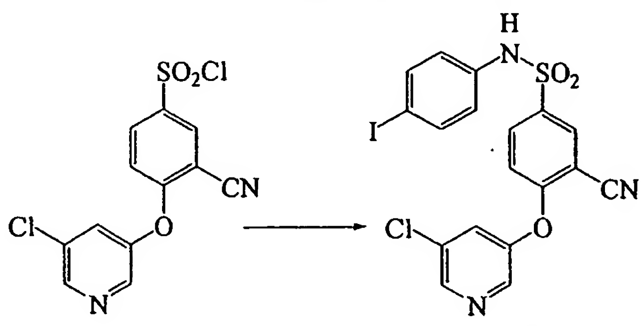


2.1 **34.1**

Aniline **2.1** (3.11 g, 12.69 mmol) was converted to the corresponding sulfonyl chloride according to the procedure of R. V. Hoffman (*Org. Syn. Coll. Vol.*, VII, 508-511), yielding 770 mg (18%) of **34.1** as a white solid. MS ESI m/e: 331.0 (M + H)

EXAMPLE 35

This example illustrates the synthesis of compound **35.1**.



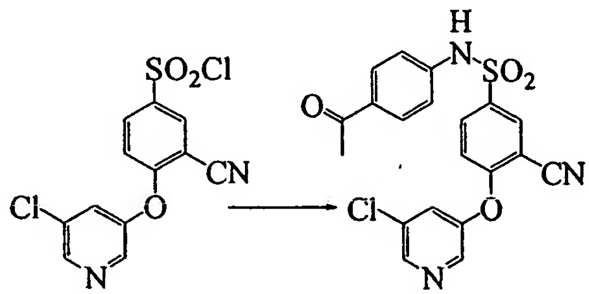
34.1 **35.1**

The title compound was prepared using the method described in Example 3, starting with 4-iodoaniline (136 mg, 0.6197 mmol, Aldrich Chemical Co.), 5-(4-chlorosulfonyl-2-cyanophenoxy)-3-chloropyridine (136 mg, 0.4131 mmol, 34.1), pyridine (49 mg, 0.6 197 mmol), catalytic DMAP, and 3 mL of methylene chloride. The product was obtained as a white solid (187 mg, 89%).

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.57 (1H, s); 8.62 (1H, d, J=1.8 Hz); 8.60 (lH, d, J=2.2 Hz); 8.28 (1H, d, J=2.4 Hz); 8.12 (1H, d, J=2.2 Hz); 7.93 (1H, dd, J_1=8.9 Hz J_2=2.3 Hz); 7.61 (2H, dd, J_1=8 .8 Hz J_2=2.0 Hz); 7.17 (1H, d, J=9.0); 6.93 (2H, dd, J_1 = 8.8 Hz J_2=2.0 Hz). \MS ESI m/e: 509.9 (M - H).

EXAMPLE 36

This example illustrates the synthesis of compound **36.1**.



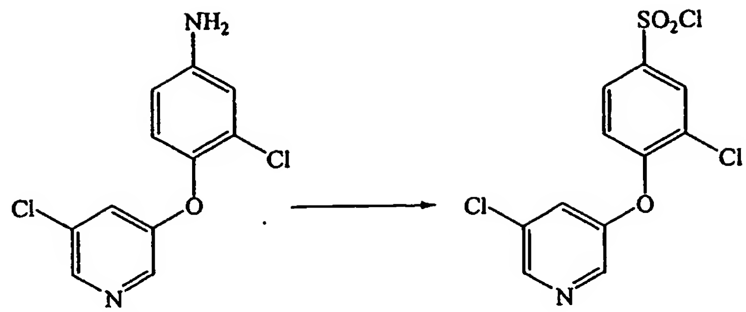
34.1 **36.1**

The title compound was prepared using the method described in Example 35, starting with 4-acetylaniline (100 mg, 0.31 mmol, Aldrich Chemical Co.), 5-(4-chlorosulfonyl-2-cyanophenoxy)-3-chloropyridine (62 mg, 0.46 mmol), pyridine (36 mg, 0.46 mmol), catalytic DMAP, and 3 mL of methylene chloride. The title compound 36.1 was obtained as a white solid (120 mg, 92%).

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.53 (1H, s); 8.58 (1H, d, J=1.9 Hz); 8.53 (1H, d, J=2.4 Hz); 8.15 (1H, d, J=2.5 Hz); 7.99 (1H, dd, J_1=4.4 Hz J_2=2.2 Hz); 7.86 (1H, dd, J_1=8.8 Hz J_2=2.5 Hz); 7.59 (2H, dd, J_1=8.8 Hz J_2=2.0 Hz); 7.13 (1H, d, J=8.7 Hz); 6.93 (2H, dd, J_i=8.8 Hz J_2=2.0 Hz); 2.61 (1H, s). MS ESI m/e: 425.9 (M - H).

EXAMPLE 37

This example illustrates the synthesis of 5-(4-chlorosulfonyl-2-chlorophenoxy)-3-chloropyridine (**37.1**).

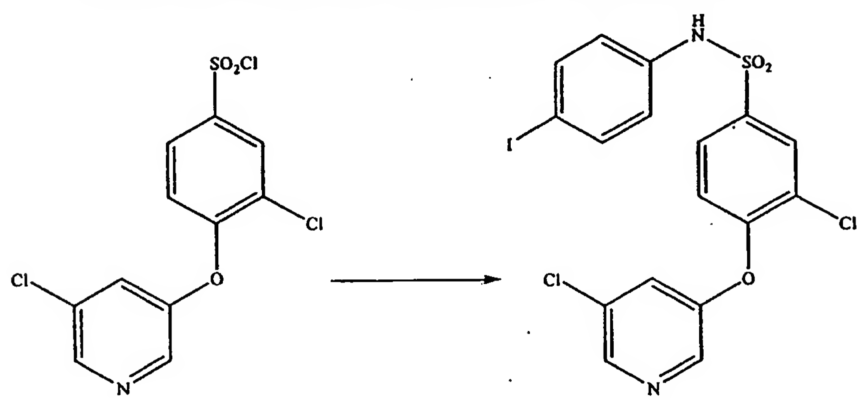


15.1 37.1

Aniline **15.1** (2.10 g, 8.24 mmol) was converted to the corresponding sulfonyl chloride **37.1**, according to the procedure of R. V. Hoffman (Org. Syn. Coll. Vol., VII, 508-511). The title compound was obtained as a slightly yellow solid (1.65 g, 59%) MS ESI m/e: 338.0 (M + H).

EXAMPLE 38

This example illustrates the synthesis of compound **38.1**.



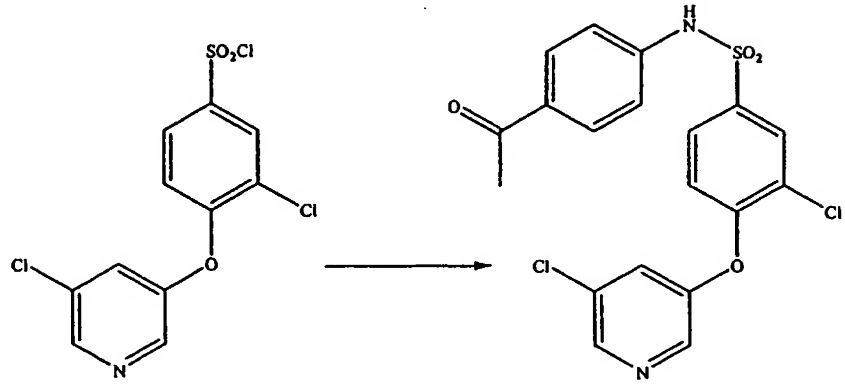
37.1 38.1

The title compound was prepared using the method described in Example 35, starting with 4-iodoaniline (101 mg, 0.46 mmol), S-(4-chlorosulfonyl-2-chlorophenoxyy3 chloropyridine (104 mg, 0.31 mmol), pyridine (35 mg, 0.46 mmol), catalytic DMAP, and 3 mL of methylene chloride. Compound **38.1** was obtained as a white solid (150 mg, 94%).

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.50 (1H, s); 8.55 (1H, d, J=2.1 Hz); 8.45 (1H, d, J=2.5 Hz); 7.93 (1H, d, J=2.2 Hz); 7.89(1H, dd, J_1=4.4 Hz J_2=2.2 Hz); 7.67 (1H, dd, J_1=8.7 Hz J_2=2.2 Hz); 7.61 (2H, dd, J_1=8 .8 Hz J_2=2.0 Hz); 7.22 (1H, d, J=8.7 Hz); 6.94 (2H, dd, J_1=8.8 Hz J_2=2.0 Hz). MS ESI m/e: 518.9 (M - H).

EXAMPLE 39

This example illustrates the synthesis of compound **39.1**.



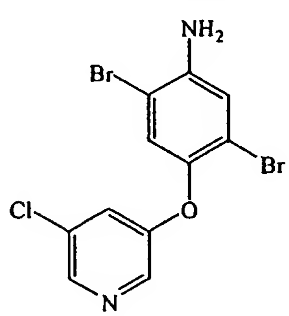
37.1 39.1

The title compound was prepared using the method of Example 38, starting with 4-acetylaniline (55 mg, 0.41 mmol), 5-(4-chlorosulfonyl-2-chlorophenoxy)-3-chloropyridine (92 mg, 0.27 mmol), pyridine (33 mg, 0.41 mmol), catalytic DMAP, and 3 mL of inethylene chloride. After workup, **39.1** was obtained as a white solid (130 mg, 93%).

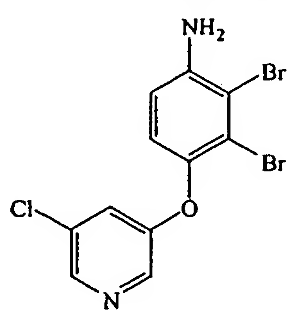
^{1}H NMR (400MHz) (d_6-DMSO) δ 10.94 (1H, s); 8.54 (1H, d, J=2.0 Hz); 8.44 (1H, d, J=2.2 Hz); 8.01 (1H, d, J=2.1 Hz); 7.90 (1H, dd, J_1=4.4 Hz J_2=2.2 Hz); 7.86 (2H, dd, J_1=8 .8 Hz J_2=1.6 Hz); 7.75 (1H, dd, J_1=8 .7 Hz J_2=2.2 Hz); 7.23 (3H, m). MS ESI m/e: 435.0 (M - H).

EXAMPLE 40

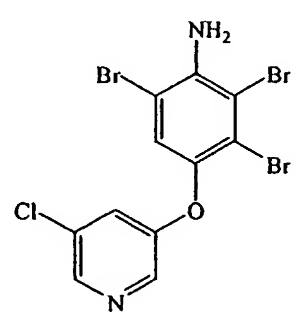
This example illustrates the preparation of 5-(4-amino-2,5-dibromophenoxy)3-chloropyridine (**40.1**), 5-(4-amino-2,3 -dibromophenoxy)-3-chloropyridine (**40.2**), and 5-(4-amino-2,3 ,5-tribromophenoxy)-3-chloropyridine (**40.3**).



40.1



40.2



40.3

To a 0.1 M solution of 3-bromo-4-(3-chloro-5-pyridyloxy)aniline (**20.1**) in acetic acid was added bromine (Aldrich). The resulting solution was stirred for two days. Most of the acetic acid was removed azeotropically using hexanes and the residue was adjusted to pH 6 using 4 M aqueous NaGH. The aqueous layer was extracted with ethyl acetate and the combined organic portions were washed with brine (2X), dried over sodium sulfate, filtered and concentrated under reduced pressure. The products were separated by chromatography to provide 5-(4-amino-2,5 -dibromophenoxy)-3-chloropyridine (**40.1**, 32%), 5-(4-amino-2,3-dibromophenoxy)-3-chloropyridine (**40.2**, 15%), and 5-(4-amino-2,3 ,5-tribromophenoxy)-3 -chloropyridine (**40.3**, 13%).

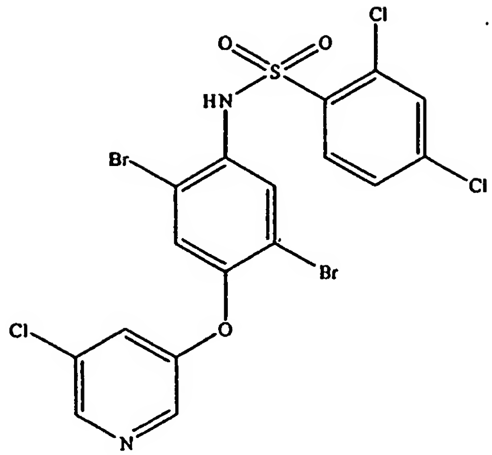
40.1: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.35 (d, J = 1.5 Hz, 1H), 8.22 (d, J = 2.5 Hz, 1H), 7.46 (d, J = 1.0 Hz, 1H), 7.39 (dd, J = 2.8, 2.6 Hz, 1H), 7.14 (s, 1H), 5.6 (s, 2H). MS (EI): *m/z* 383 (18, M+H), 382 (10, M+H), 381 (75, M+H), 380 (15, M+H), 379 (100, M+H), 378 (7, M+H), 377 (50, M+H).

40.2: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.34 (d, J = 2 Hz, 1H), 8.21 (d, J = 2.6 Hz, 1H), 7.36 (dd, J = 2.4, 2.2 Hz, 1H), 7.32 (dd, J = 8.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 5.7 (s, 2H). MS (EI): *m/z* 383 (18, M+H), 382 (10, M+H), 381 (75, M+H), 380 (15, M+H), 379 (100, M+H), 378 (7, M+H), 377 (50, M+H).

40.3: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.36 (d, J = 2.2 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 7.63 (s, 1H), 7.48 (dd, J = 2.4, 1.9 Hz, 1H), 5.65 (s, 2H). MS (EI): *m/z* 463 (10, M+H), 462 (5, M+H), 461 (50, M+H), 460 (12, M+H), 459 (100, M+H), 458 (12, M+H), 457 (85, M+H), 456 (5, M+H), 455 (25, M+H).

EXAMPLE 41

This example illustrates the preparation of 5-(4-(2,4-dichlorobenzene-sulfonamido)-2,5-dibromophenoxy)-3-chloropyridine (**41.1**).



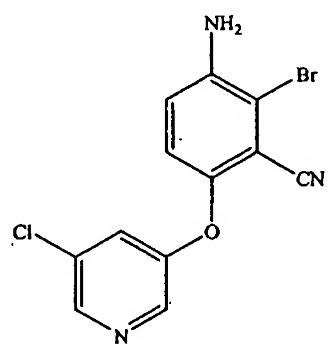
41.1

5-(4-(2,4-dichlorobenzenesulfonamido)-2,5-dibrOinOphenOxy)-3-chloropyridine was prepared in 39% yield from **40.1** and 2,4-dichlorobenzenesulfonyl chloride using the method of Example 3.

^{1}H NMR (400MHz, DMSO-d_6) δ 10.6 (s, 1H), 8.47 (bs, 1H), 8.33 (bs, 1H), 7.9 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.68 (bs, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.57 (s, 1H 7.52 (s, 1H). MS (EI): *m/z* 593 (6, M+H), 592 (4, M+H), 591 (27, M+H), 590 (10, M+H) 589 (50, M+H), 588 (10, M+H), 587 (45, M+H), 586 (3, M+H), 585 (17, M+H).

EXAMPLE 42

This example illustrates the preparation of 5-(4-amino-2-cyano-3-bromophenoxy))-3-chloropyridine (**42.1**).



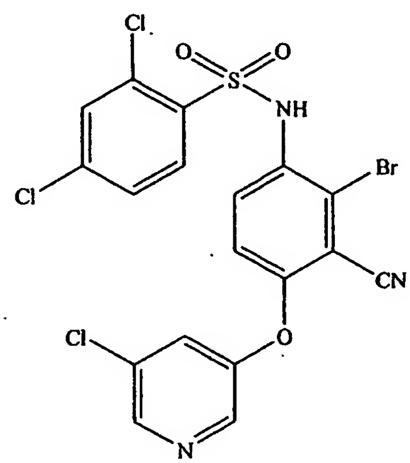
42.1

3-Cyano-4-(3-chloro-5-pyridyloxy)aniline (see Example 2) was combined with bromine in acetic acid in a manner similar to that described in Example 40 to produce 5-(4-amino-2-cyano-3-bromophenoxy)-3-chloropyridine (37%) after chromatography.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.44 (d, J = 1.8 Hz, 1H), 8.37 (d, J = 2.2 Hz, 1H), 7.7 (dd, J = 2.2, 1.8 Hz, 1H), 7.13 (1/2ABq, J = 9.1 Hz, 1H), 7.11 (1/2ABq, J = 9.1 Hz, 1H), 5.83 (s, 2H). MS (EI): *m/z* 328 (30, M+H), 327 (13, M+H), 326 (100, M+H),325 (10, M+H), 324 (75, M+H).

EXAMPLE 43

This example illustrates the synthesis of 5-(4-(2,4-dichlorobenzene-sulfonamido)-2-cyano-3-bromophenoxy)-3-chloropyridine (**43.1**).



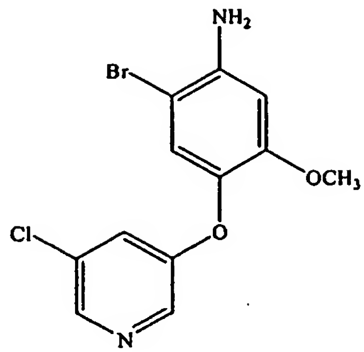
43.1

5-(4-(2,4-dichlorobenzenesulfonamido)-2-cyano-3-bromophenoxy)-3-chloropyridine was prepared in 28% yield from **42.1** and 2,4-dichlorobenzenesulfonyl chloride using the method of Example 3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 8.59 (d, J = 1.6 Hz, 1H), 8.53 (d, J = 2 Hz, 1H), 8.05 (bs, 1H), 7.9 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.6 (dd, J = 8.4, 1.6 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 9.2 Hz, 1H). MS (EI): *m/z* 537 (20, M+H), 535 (73, M+H), 533 (100, M+H), 53 1(52, M+H).

EXAMPLE 44

This example illustrates the preparation of 5-(4-amino-5-bromo-2-methoxyphenoxy))-3-chloropyridine (**44.1**).



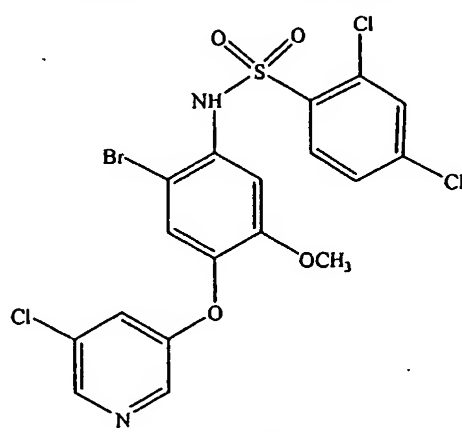
44.1

To a 0.2M solution of 5-(4-amino-2-methoxyphenoxy)-3-chloropyridine (200 mg, 0.8 mmol, **22.1**) in CH_2Cl_2 at 0 °C was added 2,4,4,6-tetrabromo-2,5-cyclohexadieneone (334 mg, 0.82 mmol, Lancaster). The resulting solution was stirred for 21 hours at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed twice with a 2M solution of aqueous sodium hydroxide (50 mL), once with brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was purified by column chromatography (0-2% MeOH in CH_2Cl_2) to furnish 133 mg (50%) of the title compound as a brown solid.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.27 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 2.6 Hz, 1H), 7.26 (dd, J = 2.3, 1.9 Hz, 1H), 7.24 (s, 1H), 6.64 (s, 1H), 5.38 (s, 2H), 3.65 (s, 3H). MS (EI): *m/z* 329 (80, M+H), 330 (12, M+H), 331 (100, M+H), 332 (16, M+H), 333 (28, M+H), 334 (4, M+H).

EXAMPLE 45

This example illustrates the preparation of 5-(4-(2,4-dichlorobenzene-sulfonainido)-5-bromo-2-methoxyphenoxy)-3-chloropyridine (**45.1**).



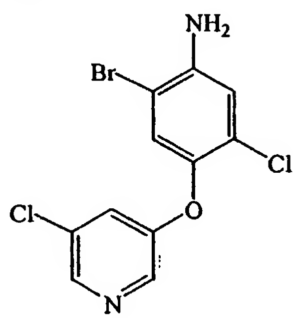
45.1

5-(4-(2,4-dichlorobenzenessulfonamido)-5-bromo-2-methoxyphenoxy)-3-chloropyridine was prepared in 25% yield from **44.1** and 2,4-dichlorobenzenesulfonyl chloride using the method of Example 3.

^{1}H NMR (400MHz, DMSO-d_6) δ 10.4 (s, 1H), 8.36 (d, J = 1.8 Hz, 1H), 8.2 (d, J = 2.5 Hz, 1H), 7.9 (d, J = 8.6 Hz, 1H), 7.9-7.65 (m, 1H), 7.68 (bs, 1H), 7.59 (dd, J = 8.6, 2.2 Hz, 1H), 7.45 (s, 1H), 7.42 (dd, J = 2.4, 1.9 Hz, 1H), 6.99 (s, 1H), 3.65 (s, 3H). MS (EI): *m/z* 537 (58, M+H), 538 (10, M+H), 539 (100, M+H), 540 (20, M+H), 541 (70, M+H), 542 (15, M+H), 543 (25, M+H).

EXAMPLE 46

This example illustrates the preparation of 5-(4-amino-5-bromo-2-chlorophenoxy))-3-chloropyridine (**46.1**).



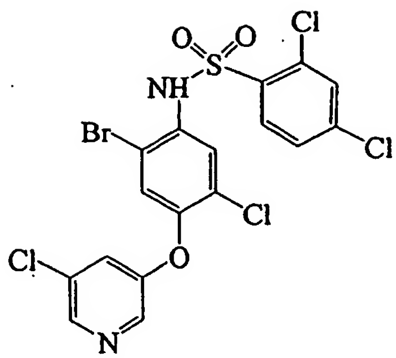
46.1

5-(4-Amino-5-bromo-2-chlorophenoxy)-3-chloropyridine was synthesized (43%) in a similar manner as described by Example 44 using 3-chloro-4-(3-chloro-5-pyridyloxy)aniline (**15.1**).

^{1}H NMR (400MHz, DMSO-d_6) δ 8.35 (d, J = 1.9 Hz, 1H), 8.23 (d, J = 2.5 Hz, 1H), 7.48 (s, 1H), 7.41 (dd, J = 2.4, 2.2 Hz, 1H), 6.98 (s, 1H), 5.62 (s, 2H). MS (EI): *m/z* 333 (55, M+H), 334 (12, M+H), 335 (90, M+H), 336 (12, M+H), 337 (40, M+H), 338 (5, M+H).

EXAMPLE 47

This example illustrates the preparation of 5-(4-(2,4-dichlorobenzene-sulfonamido)-5-bromo-2-chlorophenoxy)-3-chloropyridine (**47.1**).



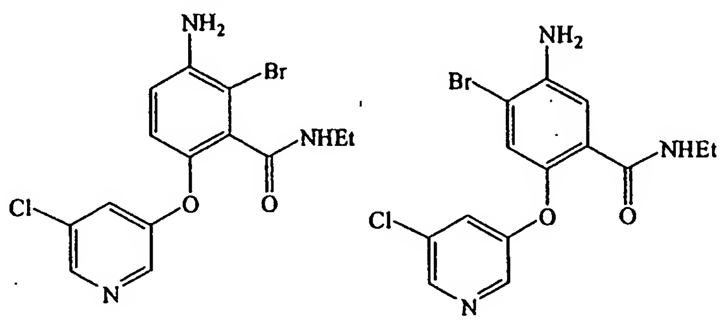
47.1

5-(4-(2,4-dichlorobenzenesulfonamido)-5-bromo-2-chlorophenoxy)-3-chloropyridine was prepared in 17% yield from 46.1 and 2,4-dichlorobenzenesulfonyl chloride using the method of Example 3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 8.47 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 2.6 Hz, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.7 (dd, J = 2.3, 2.2 Hz, 1H), 7.6 (dd, J = 8.5, 2.0 Hz, 1H), 7.55 (s, 1H), 7.47 (s, 1H). MS (EI): *m/z* 539 (40, M-H), 540 (10, M-H), 541 (100, M-H), 542 (20, M-H), 543 (80, M-H), 544 (25, M-H), 545 (35, M-H), 546 (5, M-H).

EXAMPLE 48

This example illustrates the preparation of 5-(3-chloro-4-amino-2-(N-ethylcarboxamidophenoxy))-3-chloropyridine (48.1) and 5-(5-chloro-4-amino-2-(N-ethylcarboxamidophenoxy))-3-chloropyridine (48.2).



48.1 48.2

To a 0.1M solution of 5-(4-amino-2-(N-ethylcarboxamidophenoxy))-3-chloropyridine, (1 g, 3.6 mmol, prepared as described in U.S.S. N. 09/234,327) in AcOH was added bromine (194 μL, 3.8 mmol) and the resulting solution was stirred for 2 days. Most of the AcOH was azeotropically removed using hexanes and the resulting solution

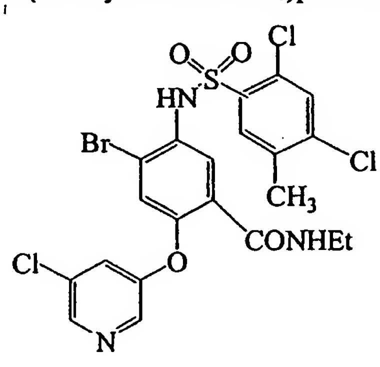
was adjusted to ph 6 using a 4M aqueous solution of NaOH. The aqueous layer was extracted three times with EtOAc (50 mL) and the combined organic layers were washed twice with an aqueous brine solution (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was purified by chromatography (50-100% EtOAc in hexanes) to separate the products **48.1** and **48.2** from the starting materials and dibrominated materials. The desired products were then rechroinatographed (1-3% MeOH in CH_2Cl_2) to furnish 478 mg (36%) of 48.1 and 198 mg (15%) of 48.2 as white solids.

48.1: ^{1}H NMR (400MHz, DM50-d_6) δ 8.37 (t, J = 5.2 Hz, 1H), 8.3 (bs, 1H), 8.24 (d, J = 2.2 Hz, 1H), 7.38 (m, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 3.1 (pentet, J = 7.0 Hz, 2H), 0.91 (t, J = 7.1 Hz, 3H). MS (EI): *m/z* 370 (80, M+H), 371 (15, M+H), 372 (100, M+H), 373 (18, M+H), 374 (25, M+H).

48.2: ^{1}H NMR (400MHz, DMSO-d_6) δ 8.3 (d, J = 1.75 Hz, 1H), 8.23 (t, J = 5.4 Hz, 1H), 8.2 (d, J = 2.0 Hz, 1H), 7.34-7.28 (m, 2H), 6.99 (d, J = 1.6 Hz, 1H), 3.08 (pentet, J = 7.2 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H). MS (EI): *m/z* 370 (80, M+H), 371 (15, M+H), 372 (100, M+H), 373 (18, M+H), 374 (25, M+H).

EXAMPLE 49

This example illustrates the preparation of 5-(5-bromo-4-(2,4-dichloro-5-methylbenzenesulfonamido)-2-(N-ethylcarboxamido)phenoxy)-3-chloropyridine (**49.1**).



49.1

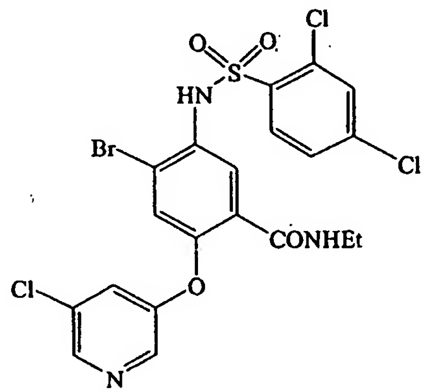
The title compound was prepared in 67% yield from **48.1** and 2,4-dichloro-5-inethylbenzenesulfonyl chloride using the method of Example 3.

^{1}H NMR (400MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.48 (d, J = 2.1 Hz, 1H), 8.35 (t, J = 5.4 Hz, 1H), 8.31 (d, J = 2.5 Hz, 1H), 7.85 (bs, 2H), 7.6 (dd, J = 2.3, 2.2 Hz, 1H), 7.41 (s, 1H), 7.39 (s, 1H), 3.14 (pentet, J = 7.2 Hz, 2H), 2.34 (s, 3H), 0.94 (t, J = 7.2

Hz, 3H). MS (EI): *m/z* 597 (8, M-H), 596 (25, M-H), 595 (20, M-H), 594 (70, M-H), 593 (30, M-H), 592 (100, M-H), 591 (12, M-H), 590 (50, M-H).

EXAMPLE 50

This example illustrates the preparation of 5-(5-bromo-4-(2,4-dichlorobenzenesulfonamido)-2-(N-ethylcarboxamido)phenoxy)-3-chloropyridine (**50.1**).



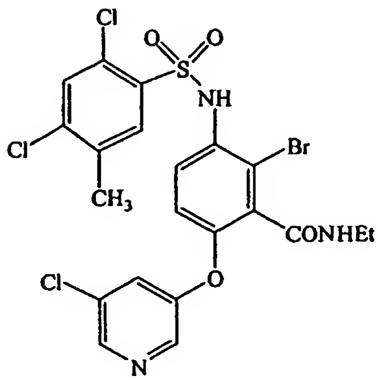
50.1

The title compound was prepared in 28% yield from **48.1** and 2,4-dichloro-benzenesulfonyl chloride using the method of Example 3.

^{1}H NMR (400MHz, DMSO-d_6) δ 10.5 (s, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.34 (t, J = 5.6 Hz, 1H), 8.31 (d, J = 2.3 Hz, 1H), 7.9 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.62 (dd, J = 2.4, 2.1 Hz, 1H), 7.59 (dd, J = 8.6, 2.2 Hz, 1H), 7.41 (s, 1H), 7.38 (s,1H), 3.14 (pentet, J = 7.0 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). MS (EI): *m/z* 585 (8, M+H), 584 (25, M+H), 583 (18, M+H), 582 (70, M+H), 581 (25, M+H), 580 (100, M-H), 579 (12, M+H), 578 (50, M+H).

EXAMPLE 51

This example illustrates the preparation of 5-(3-bromo-4-(2,4-dichloro-5-methylbenzenesulfonamido)-2-(N-ethylcarboxamido)phenoxy)-3-chloropyridine (**51.1**).



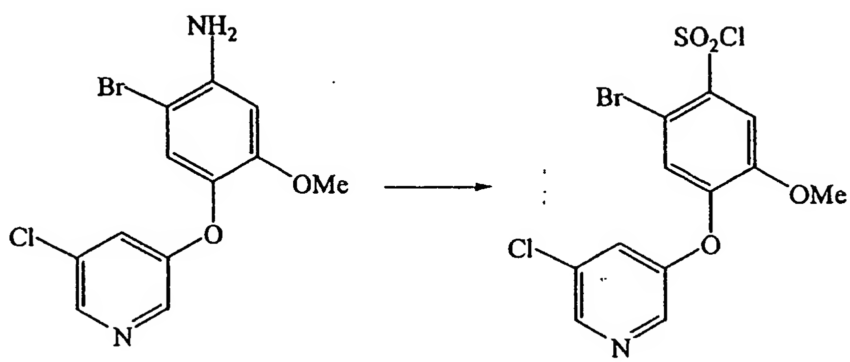
51.1

The title compound was prepared in 37% yield from **48.2** and 2,4-dichloro-5-methylbenzenesulfonyl chloride using the method of Example 3.

^{1}H NMR (400MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.55 (t, 1H), 8.42 (d, 1H), 8.31 (d, 1H), 7.89 (s, 1H), 7.88 (s, 1H), 7.6 (dd, 1H), 7.12 (d, 1H), 7.02 (d, 1H), 3.14 (pentet, 2H), 2.35 (s, 3H), 0.94 (t, 3H). MS (EI): *m/z* 599 (8, M+H), 598 (25, M+H), 597 (18, M+H), 596 (70, M+H), 595 (25, M+H), 594 (100, M-H), 593 (12, M+H), 592 (50, M+H).

EXAMPLE 52

This example illustrates the synthesis of 5-(5-bromo-4-chlorosulfonyl-2-methoxyphenoxy)-3-chloropyridine (**52.1**).

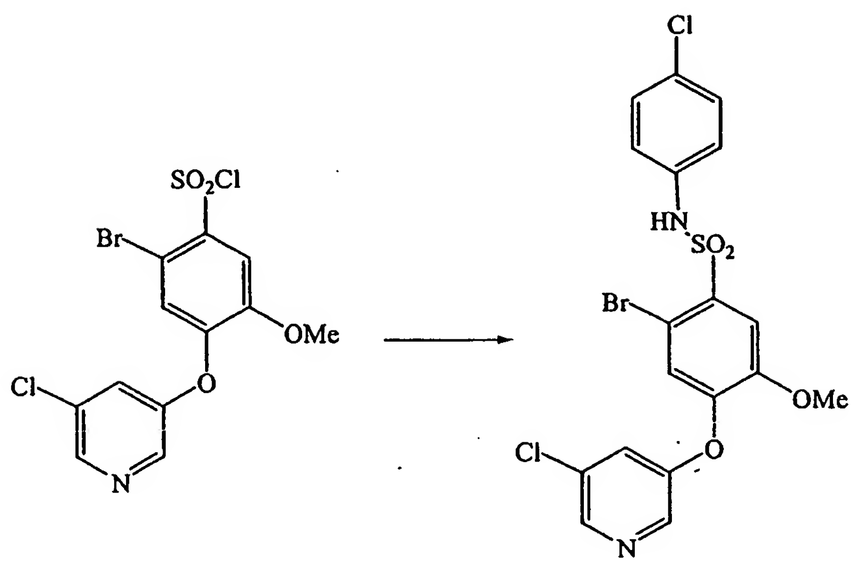


44.1 **52.1**

Compound **44.1** (1.20 g, 3.66 mmol) was converted to the title compound using the general procedure of R. V. Hoffman (Org. Syn. Coll. Vol., VII, 508-511), to provide 1.26 g (84%) of **52.1** as a clear oil which was carried on without purification. MS ESI m/e: 412.0(M+H).

EXAMPLE 53

This example illustrates the preparation of **53.1**.



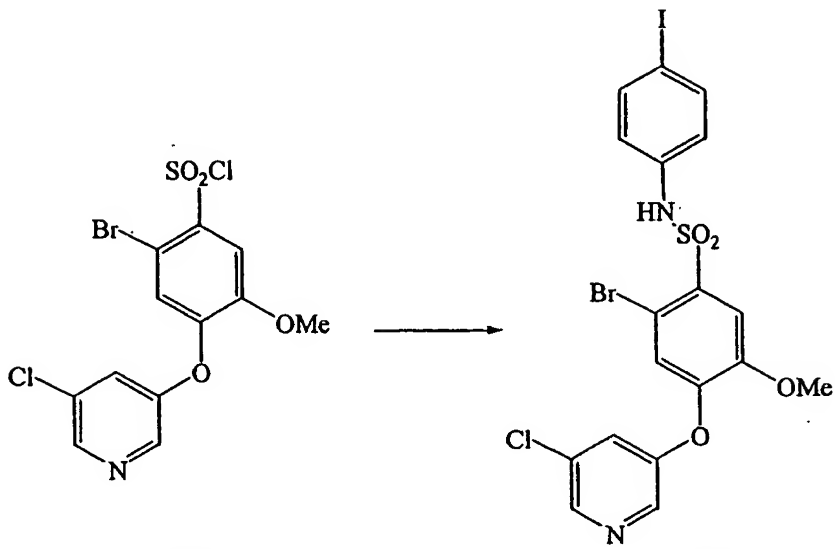
52.1 **53.1**

4-Chloroaniline (73 mg, 0.57 mmol, Aldrich Chemical Co.), 5-(5-bromo-4-chlorosulfonyl-2-methoxyphenoxy)-3-chloropyridine (236 mg, 0.57 mmol), pyridine (45 mg, 0.57 mmol), catalytic DMAP, and 2 mL of methylene chloride were combined using the general method of Example 35. The title compound was obtained (245 mg, 85%) as a white solid.

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.80 (1H, s); 8.43 (1H, d, J=2.0 Hz); 8.30 (1H, d, J=2.4 Hz); 7.74 (1H, s); 7.64 (1H, dd, J=4.4 Hz, 2.2 Hz); 7.52 (1H, s); 7.31 (2H, dd, J=8.8 Hz, 2.1 Hz); 7.14 (1H, dd, J=8.8 Hz, 2.1 Hz); 3.83 (3H, s). MS ESI m/e: 435.0 (M - H).

EXAMPLE 54

This example illustrates the preparation of **54.1**.



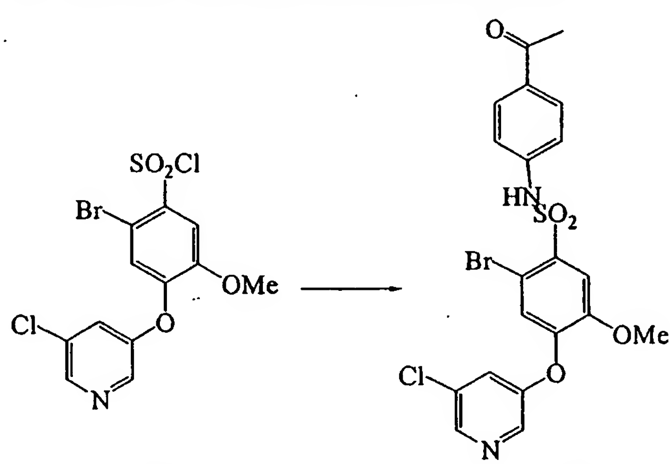
52.1 **54.1**

In a manner similar to that described in Example 53, 4-iodoaniline (83 mg, 0.38 mmol), 5-(5-bromo-4-chlorosulfonyl-2-methoxyphenoxy)-3-chloropyridine (155 mg, 0.38 mmol), pyridine (30 mg, 0.38 mmol), catalytic DMAP, and 2 mL of methylene chloride were combined and stirred. After workup, the title compound was obtained (162 mg, 73%) as a white solid.

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.80 (1H, s); 8.43 (1H, d, J=2.0 Hz); 8.31 (1H, d, J=2.4 Hz); 7.75 (1H, s); 7.64 (1H, dd, J=4.4 Hz, 2.2 Hz); 7.58 (2H, m); 7.51 (1H, s) 6.95 (1H, dd, J=8.6 Hz, 2.2 Hz); 3.84 (3H, s). MS ESI m/e: 592.8 (M - H).

EXAMPLE 55

This example illustrates the preparation of **55.1**.



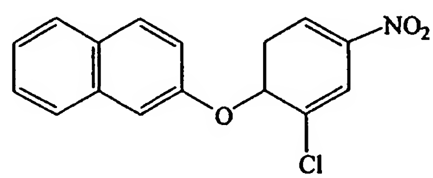
52.1 **55.1**

In a manner similar to that described in Example 53, 4-acetylaniline (69 mg, 0.51 mmol), 5-(5-bromo-4-chlorosulfonyl-2-methoxyphenoxy)-3-chloropyridine (210 mg, 0.51 mmol), pyridine (40 mg, 0.51 mmol), catalytic DMAP, and 2 mL of methylene chloride were combined and stirred. After workup, the title compound was obtained (192 mg, 74%) as a white solid.

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.80 (1H, s); 8.43 (1H, d, J=2.0 Hz); 8.31 (1H, d, J=2.4 Hz); 7.75 (1H, s); 7.64 (1H, dd, J=4.4 Hz, 2.2 Hz); 7.58 (2H,m); 7.51 (1H, s) 6.95 (1H, dd, J=8.6 Hz, 2.2 Hz); 3.84 (3H, s). MS ESI in/e: 509.0 (M - H).

EXAMPLE 56

This example illustrates the preparation of 3-chloro-4-(2-naphthylxoy)nitrobenzene (**56.1**).



56.1

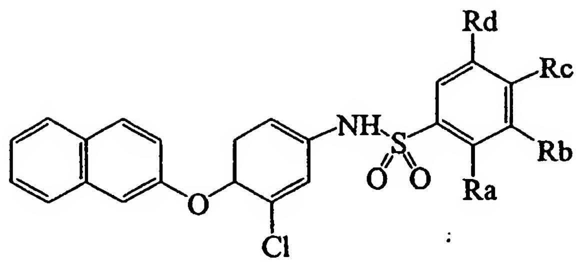
To a 250 mL flask, were added 3-chloro-4-fluoro-nitrobenzene (Aldrich)(5.0 g, 28 mmol), 2-naphtol (Aldrich)(4.Sg, 31 mmol), Cs_2CO_3 (Aldrich)(9.7g, 30 mmol) and DME (80 mL). The mixture was heated at 100 °C overnight. After removal of DMF under vacuum, the mixture was poured into water and extracted with dichloromethane. The organic solution was then washed with brine, dried over magnesium sulfate. After filtration, the filtrate was concentrated under vacuum to give a crude product, which was then chromatographed with eluent (30% dichloromethane / hexanes) to give the title compound (6.8 g, 24 mmol, 86%).

EXAMPLE 57

This example illustrates the preparation of compounds **57.1**, **57.2**, **57.3** and **57.4**.

Compound **56.1** was reduced to the corresponding aniline derivative (**57.1**) using the procedure of Example 2, and converted to the compounds in Table 8 using commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

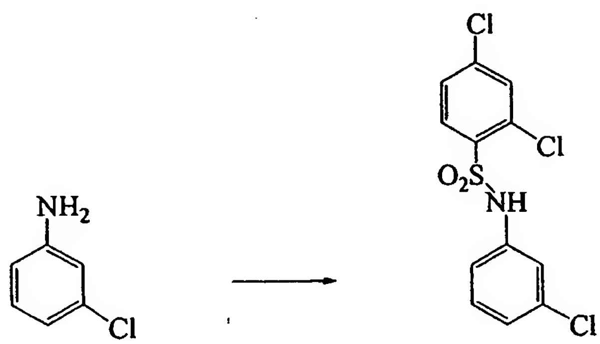
Table 8



	Ra	Rb	Rc	Rd	m/e
57.2	Cl	H	Cl	H	476
57.3	Cl	H	I	H	534
57.4	H	H	OCH_3	H	438

EXAMPLE 58

This illustrates the synthesis of 3-chloro-(2,4-dichlorobenzene-sulfonainido)benzene (**58.1**).



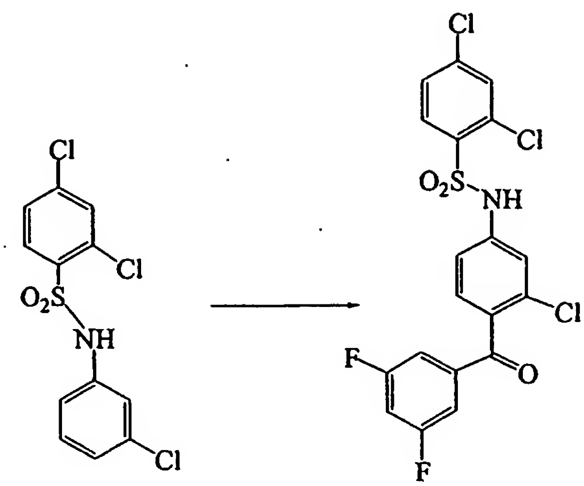
58.1

The title compound was prepared using the method described in Example 3, starting with 800 mg (6.29 mmol) of 3-chloroaniline, 1.53 g (6.29 mmol) of 2,4-dichlorosulfonylchloride, 497 mg (6.29 mmol) of pyridine, catalytic DMAP, and 10 mL of methylene chloride. The title compound was obtained as a white foam (928 mg, 44%).

MS ESI m/e: 334.0 (M - H).

EXAMPLE 59

This example illustrates the synthesis of compound **59.1**.



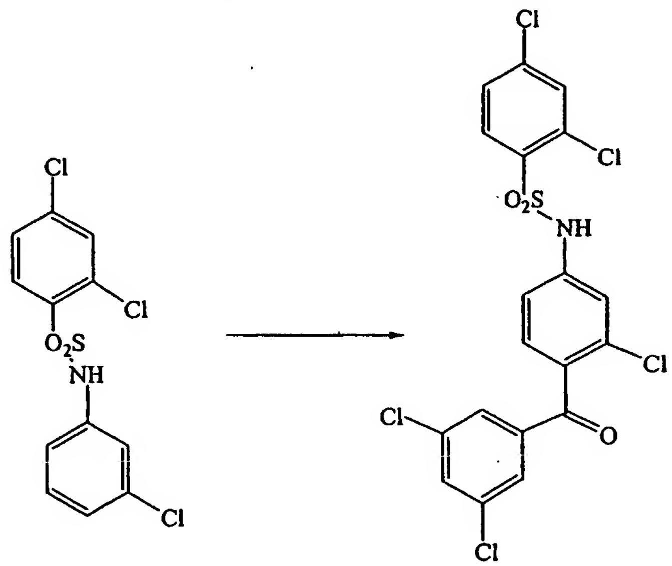
58.1 59.1

A round-bottomed flask was charged with 330 mg (0.99 mmol) of 3-chloro-(2,4-dichlorobenzenesulfonamido)benzene (**58.1**), 397 mg (2.97 mmol, Aldrich Chemical Co.) of anhydrous aluminum trichloride, and 2 mL of dry dichloroethane. Then 210 mg (1.19 mmol, Aldrich Chemical Co.) of 3,5-difluorobenzoyl chloride was added dropwise and the deep red solution was allowed to stir at room temperature overnight. The reaction was then diluted with 30 mL of methylene chloride, washed consecutively with 2N HCl and brine, dried over $MgSO_4$, and concentrated to a dark oil. This was further purified by silica gel flash chromatography (eluting with 1:24 ethyl acetate:methylene chloride). The resulting clear glaze was recrystallized from ether/hexanes to yield 273 mg (58%) of a white solid.

^{1}H NMR (400MHz) (d_6-DMSO) δ 8.15 (1H, d, J=8.5 Hz); 7.91 (1H, d, J=2.1 Hz); 7.68 (1H, dd, J=8.6 Hz, 2.1 Hz); 7.63 (1H, t, J=8.6 Hz); 7.46 (1H, d, J=8.4 Hz); 7.31 (2H, dd, J=7.8 Hz, 2.1 Hz); 7.23 (1H, d, J=1.9 Hz); 7.17 (1H, dd, J=8.4 Hz, 2.2 Hz). MS ESI m/e: 473.9 (M - H).

EXAMPLE 60

This illustrates the synthesis of compound 60.1.



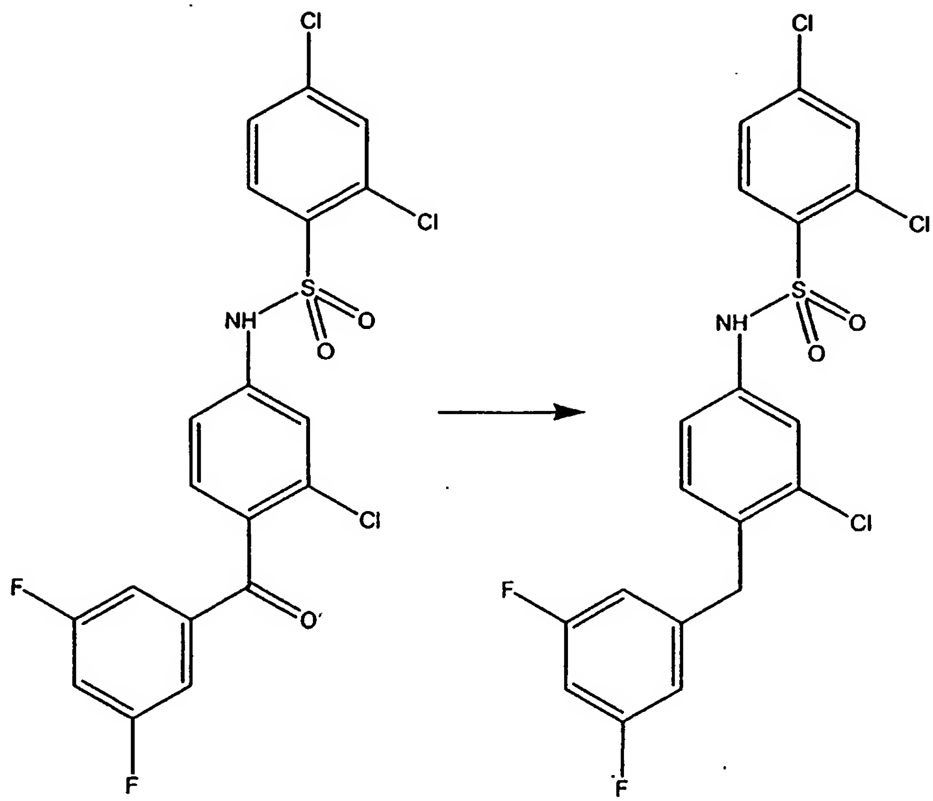
58.1 60.1

The title compound was prepared using the method of Example 59, starting with 286 mg (0.85 mmol) of 3-chloro-(2,4-dichlorobenzenesulfonamido)benzene (58.1), 341 mg (1.02 mmol) of anhydrous aluminum trichloride, 214 mg (1.02 mmol, Aldrich Chemical Co.) of 3,5-dichlorobenzoyl chloride, and 2 mL of dry dichloroethane. The title compound was obtained as a white solid (139 mg, 32%).

^{1}H NMR (400MHz) (d_6-DMSO) δ 11.49 (1H, s) 8.15 (1H, d, J=8.6 Hz); 7.97 (1H, d, J=3.8 Hz); 7.91 (1H, d, J=2.1 Hz); 7.69 (1H, dd, J=8.5 Hz, 2.0 Hz); 7.58 (2H, d, J=1.9 Hz); 7.47 (1H, d, 1=8.4 Hz); 7.24 (1H, d, J=2.0 Hz); 7.17 (1H, dd, J=8.4 Hz, 2.1 Hz). MS ESI m/e: 505.9 (M - H).

EXAMPLE 61

This illustrates the synthesis of compound 61.1.



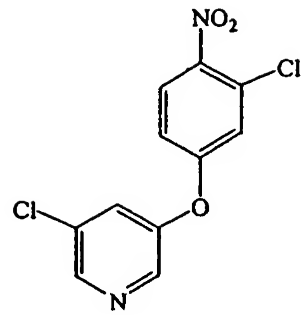
59.1 61.1

Biaryl ketone **59.1** (103 mg, 0.22 mmol) was reduced to the methylene compound **61.1** according to the procedure of West, *et. al., J. Org. Chem.*, 38(15):2675-2681 (1973). The title compound was obtained as a white solid (86 mg, 86%).

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.96 (lH, s) 8.05 (1H, d, J=8.6 Hz); 7.87 (1H, d, J=2.0 Hz); 7.63 (1H, dd, J=8.5 Hz, 2.1 Hz); 7.23 (1H, d, J=8.5 Hz); 7.14 (1H, d, J=2.2 Hz); 7.02 (2H, m); 7.17 (2H, m). MS ESI m/e: 460.0 (M - H).

EXAMPLE 62

This example illustrates the preparation of 2-chloro-4-(3-chloro-5-pyridyloxy)-nitrobenzene **62.1**.



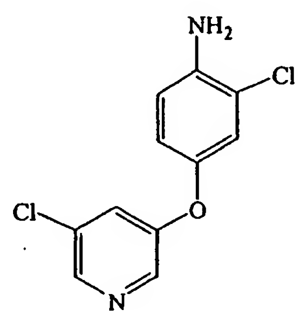
62.1

5-Chloro-3-pyridinol (5 g, Aldrich) and 2,4-dichloronitrobenzene (7.4 g, Aldrich) were combined as described in Example 1. The title compound was isolated as the minor product using gravity chromatography on silica eluting with 10% ethyl acetate / hexanes.

^{1}H NMR (400 MHz) (DMSO-d_6) δ 8.53 (s, 1H); 8.4 (s, 1H); 8.0 (d, *J*=8.9 Hz, 1H); 7.44 (t, *J*=1.9 Hz, 1H); 7.26 (d, 1=1.5 Hz, 1H); 7.14 (d, 1=2.7 Hz, 1H); 6.99 (dd, 1=9.0, 2.6 Hz, 1H) 1.6 (impurity).

EXAMPLE 63

This example illustrates the preparation of 2-chloro-4-(3-chloro-5-pyridyloxy)-aniline **63.1**.



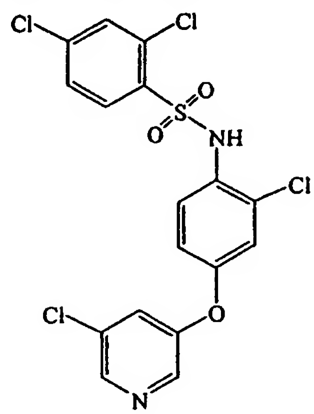
63.1

Compound **62.1** was reduced using the method of Example 2 to provide the title compound as a yellow solid.

^{1}H NMR (400 MHz) (DMSO) δ 8.33 (d, J-2.1 Hz, 1H); 8.25 (d, *J*=2.4 Hz, 1H); 7.41 (t, *J*=2.2 Hz, 1H); 7.12 (d, *J*=2.6 Hz, 1H); 6.91 (dd, *J*=2.6, 8.8 Hz, 1H); 6.84 (d, *J*=8.8 Hz, 1H); 5.35 (s, 2H).

EXAMPLE 64

This example illustrates the preparation of **64.1**.

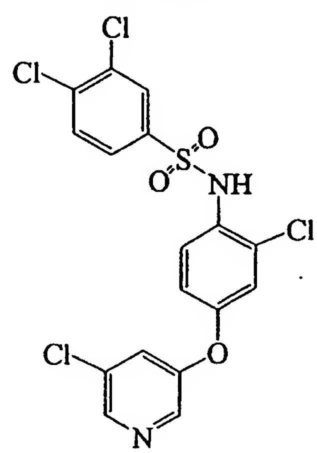


64.1

Compound **63.1** and 2,4-dichlorobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified by flash chromatography on silica eluting with dichloromethane. The resulting product was then triturated in diethyl ether/hexanes to furnish the title compound as a white solid. MS ESI m/e: 461 (M-H).

EXAMPLE 65

This example illustrates the preparation of **65.1**.



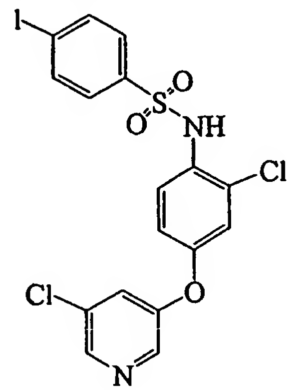
65.1

Compound **63.1** and 3,4-dichlorobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified by flash chromatography on silica eluting with 5% ethyl acetate/

dichloromethane. The resulting product was then triturated in hexanes to furnish the title compound as a white solid. MS ESI m/e: 461 (M-H).

EXAMPLE 66

This example illustrates the preparation of **66.1**.

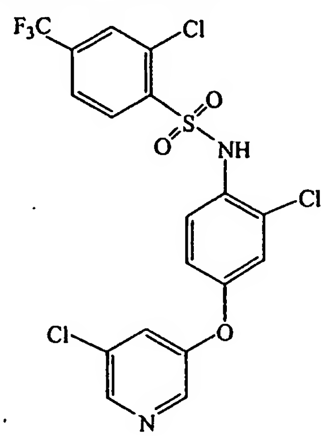


66.1

Compound **63.1** and 4-iodobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified by flash chromatography on silica eluting with dichloroinethane. The resulting product was then triturated in hexanes to furnish the title compound as a white solid. MS ESI m/e: 519 (M-H).

EXAMPLE 67

This example illustrates the preparation of **67.1**.



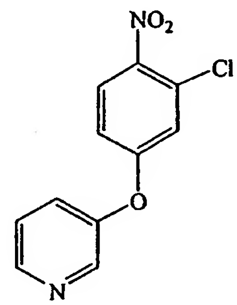
67.1

Compound **63.1** and 2-chloro-4-trifluoroinethylbenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The

crude product was purified by flash chromatography on silica eluting with 5% ethyl acetate / dichloroinethane. The resulting product was then triturated in hexanes to furnish the title compound as a white solid. MS ESI m/e: 495 (M-H).

EXAMPLE 68

This example illustrates the preparation of 2-chloro-4-(3-pyridyloxy)nitrobenzene (**68.1**).



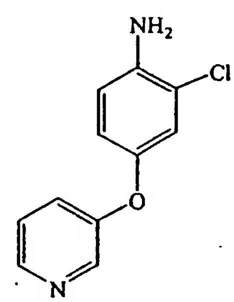
68.1

2,4-Dichloronitrobenzene (10.2 g, Aldrich) and 3-hydroxypyridine (5 g, Aldrich) were combined using the method of Example 1, to provide the 0.82 g of the title compound as a yellow solid.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.58 (s, 1H); 8.52 (s, 1H); 8.0 (d, *J*=9.0 Hz, 1H); 7.44 (s, 2H); 7.10 (d, *J*=2.6 Hz, 1 H) 6.96 (dd, *J*=9.0, 6.65 Hz).

EXAMPLE 69

This example illustrates the preparation of 2-chloro-4-(3-pyridyloxy)aniline.

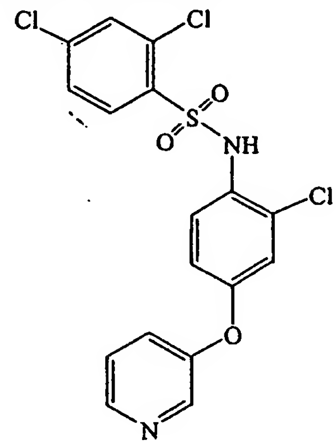


Compound **68.1** was reduced using the method of Example 2 to provide the title compound as a brown oil, which was used without further purification.

^{1}H NMR (400 MHz) (DMSO) δ 8.29-8.26 (m, 2H); 7.35 (dd, J=4.6, 8.4 Hz, 1H); 7.29-7.26 (m, 1H); 7.04 (d, *J*=2.0 Hz, 1H); 6.85-6.84 (m, 2H); 5.29 (s, 2H).

EXAMPLE 70

This example illustrates the preparation of **70.1**.

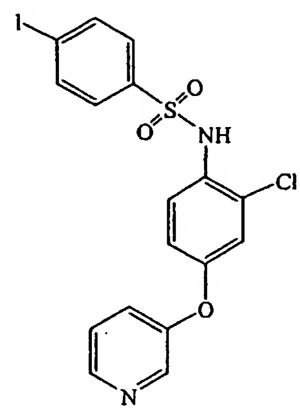


70.1

Compound **69.1** and 2,4-dichlorobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified by flash chromatography on silica eluting with 5% ethyl acetate/ dichloromethane. The resulting product was then triturated in diethyl ether to furnish the title compound as a white solid. MS ESI m/e: 429 (M-H).

EXAMPLE 71

This example illustrates the preparation of **71.1**.



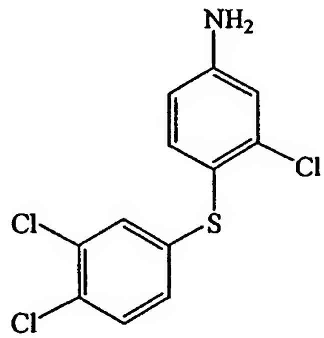
71.1

Compound **69.1** and 4-iodobenzenesulfonyl chloride were combined with pyridine and DMAP using the method described in Example 3. The crude product was purified using flash chromatography on silica eluting with 5-20% ethyl acetate/

dichloromethane. The resulting product was then triturated in diethyl ether to furnish the title compound as a white solid. MS ESI m/e: 485 (M-H).

EXAMPLE 72

This example illustrates the preparation of **72.1**.



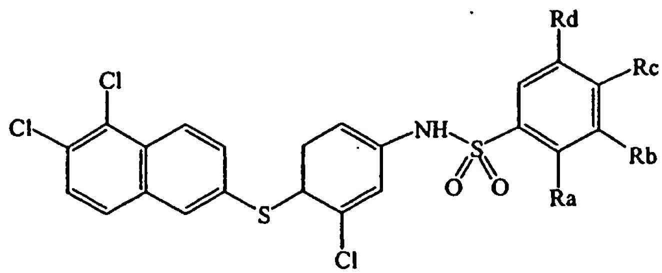
72.1

To a solution of 3,4-dichlorothiophenol (0.87 mL) and 4-fluoro-3-chloronitrobenzene (1.2 g) in THF (12 mL) was added a solution of potassium *t*-butoxide in THF (1 M, 3.7 mL). Ethanol was added to form a precipitate and the mixture was heated to dissolve the solid. The mixture was then cooled to ambient temperature and water was added. The resulting solids were colledted by filtration and washed with water. The product was dissolved in methylene chloride, dried over magnesium sulfate, filtered and concentrated to provide a yellow nitro intermediate (2.08 g).

$SnCl_2$ hexahydrate (7 g) was added to a solution of the intermediate nitro compound in ethyl acetate (40 mL) at 85°C. After 12 hr, the reaction was treated with 420 mL of 0.5 N NaOH solution and diluted with EtOAc (100 mL). The milky suspension was filtered through Celite and rinsed with additional EtOAc. The layers were separated and the water layer was extracted with additional EtOAc. The combined organic portions were dried over $MgSO_4$, filtered and concentrated under vacuum to provide the aniline derivative **72.1**, which was used without purification.

The compounds provided in Table 9 were prepared using **72.1** and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

Table 9

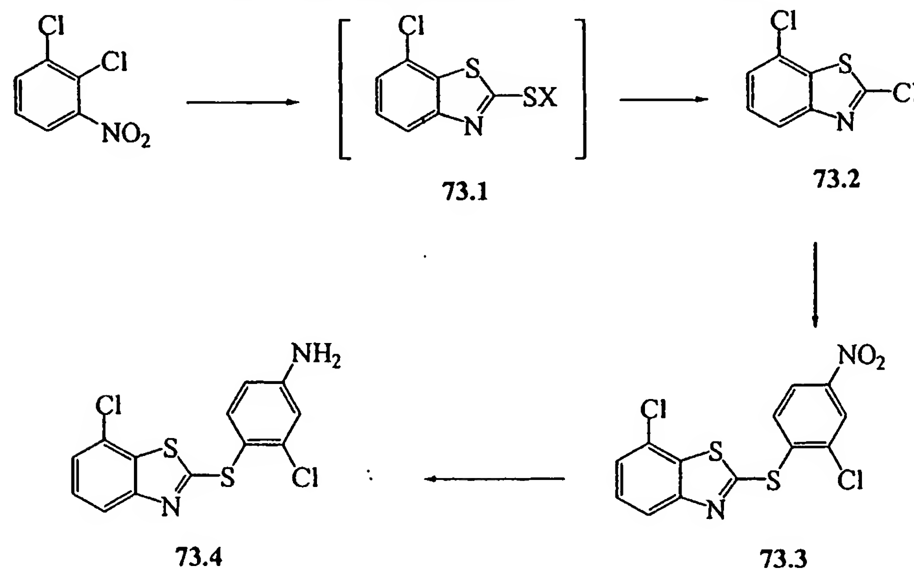


	Ra	Rb	Rc	Rd	m/e (M-H)
72.2	H	Cl	Cl	H	510
72.3	Cl	H	Cl	H	510
72.4	H	H	I	H	568

Compound **72.3** was converted to the corresponding biaryl sulfoxide (**72.5**, m/e 526) and biaryl sulfone (**72.6**, m/e 542) using an oxone procedure (see, for example, Trost, *et al., Tetrahedron Lett.*, **22**:1287 (1981) and Webb, *Tetrahedron Lett.*, **35**:3457-3460 (1994)). Similarly, compound **72.2** was converted to the biaryl sulfoxide (**72.7**, m/e 526) using a routine oxidation with mCPBA.

EXAMPLE 73

This example illustrates the preparation of **73.4** through **73.9**.



2,3 dichloronitrobenzene (19.04g) was suspended in 40% Na_2CS_3 solution in water (66 ml) with 5 ml of ethanol and heated at 130°C bath temperature for 3 days. After cooling, the residue was diluted in water and acidified with 5N HCl (caution:

foaming gas evolution). The tan solids were collected by filtration, rinsed with water and dried under vacuum to give 19.9g of an intermediate complex (**73.1**). The crude **73.1** (6.03 g) was added to neat sulfuryl chloride (20 ml) cautiously over about 5 minutes. The mixture was then heated at 50° C. The character of the solid changed but did not dissolve. The reaction was quenched by pouring onto ice. The ice mixture was stirred until the initial heavy dark oil solidified. The solids were collected by filtration, dissolved in ethyl ether and washed with water. The product was purified by flash chromatography using hexane, then 20% methylene chloride/hexane to afford 3.2 g of a 2,7-dichlorobenzothiazole (**73.2**) as a low melting solid.

^{1}H NMR ($CDCl_3$) δ 7.823 (d, J=8.4 Hz), 7.417 (t, J=8.4 Hz), 7.371 (d, J=8.4 Hz). Anal. calc: 41.20% C, 1.48% H, 6.86 % N; found: 41.06 %C, 1.46% H, 6.75% N

3-Chloro-4-mercapto nitrobenzene (prepared by the method of Price and Stacy , *J. Amer. Chem. Soc.* 68, 498-500 (1946)) (1.33 g) and 2,7-dichlorobenzothiazole (**73.2**) (1.43g) were dissolved in ethanol (20 ml) with heating. Pyridine (1.1g, 2 eq) was added. After a solid formed, additional ethanol (20 ml) was added and the mixture maintained at 50° C overnight. The solid was collected by filtration and rinsed with water. The solids were dried as a solution in methylene chloride and concentrated to afford the nitro compound **73.3** (2.22g) as an off-white solid. (mp 210-212°C)

^{1}H NMR (DMSO) δ 8.544 (d, J=2.4 Hz, 1H), 8.273 (dd, J=8.8, 2.5 Hz, 1H) 8.081 (d, J=8.6 Hz, 1H) 7.961 (dd, J=6.3, 2.4 Hz, 1H), 7.60 (m, 2H).

Using the method of example 32, the nitro derivative **73.3** was converted to the corresponding aniline (**73.4**). Flash chromatography gave a white solid. (mp 165-167°C).

^{1}H NMR (DMSO) δ 7.775 (d, J=8.4 Hz, 1H), 7.606 (d, J=8.0 Hz, 1H), 7.367 (t, J=8.0 Hz, 1H), 7.265 (d, J=8.0 Hz, 1H), 6.931 (d, J=2.0 Hz, 1H), 6.672 (dd, J=8.4, 2.4 Hz, 1H), 4.15 (br s, 2H). ESI MS 327 (M+H). Anal. calcd. 47.71% C, 2.46% H, 8.56 % N; found: 47.93 %C, 2.48 % H, 8.47% N

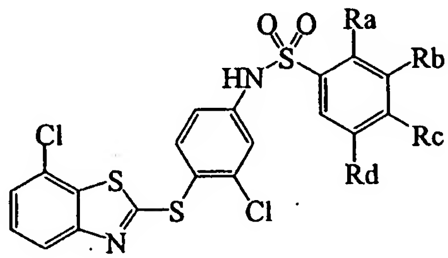
Reaction of 2-chloro-4-trifluoromethylbenzene sulfonyl chloride with aniline **73.4** according to the method of Example 3 gave sulfonamide **73.5** (see Table 10).

^{1}H NMR (DMSO) δ 11.712 (br s, 1H) 8.377 (d, J=8.4 Hz, 1H), 8.187 (d, J=2 Hz, 1H), 7.995 (dd, J=8.4, 1.2 Hz, 1H), 7.880 (d, J=8.4 Hz, 1H), 7.822 (dd, 7.2, 2.0 Hz, 1H), 7.509 (t, J=8.0 Hz, 1H), 7.474 (dd, J=7.6, 2.0 Hz, 1H), 7.443 (d, J=2.4 Hz, 1H),

7.256 (dd, J=8.8, 2.4 Hz, 1H). MS (M+H) 569; MS (M-H) 567. Anal. calcd. 42.15% C, 1.77% H, 4.92 % N; found: 42.30 %C, 1.76 % H, 4.94% N.

The additional compounds provide in Table 10 were prepared similarly using aniline **73.4** and the corresponding sulfonyl chlorides using the method of Example 3.

Table 10



	Ra	Rb	Rc	Rd	m/e (M-H)
73.5	Cl	H	CF_3	H	567
73.6	H	Cl	Cl	H	533
73.7	Cl	H	Cl	H	533
73.8	H	H	I	H	591
73.9	Cl	H	Cl	Me	547

EXAMPLE 74

The following benzenesulfonyl chlorides were prepared by the procedure of R. V. Hoffman (Org. Syn. Coll. Vol. VII, 508-511) from the corresponding commercially available anilines and used to make the indicated examples.

74a 2-chloro-4-t-butylbenzenesulfonyl chloride. yield 34% for examples 76.8 and 79.9

^{1}H NMR ($CDCl_3$) δ 8.06 (1H, d, J = 8.4 Hz), 7.62 (1H, s), 7.48 (1H, d, J = 8.4 Hz), 1.37 (9H, s). m.p. 68.8 °C.

74b 2-trifluoromethyl-4-chlorobenzenesulfonyl chloride. yield 76% as a solid.

for examples 176 and 347

^{1}H NMR ($CDCl_3$) δ 8.325 (d, J=8.4 Hz, 1H), 7.966 (br s, 1H), 7.829 (br d, J=8.4 Hz, 1H). m.p. 37.0 °C.

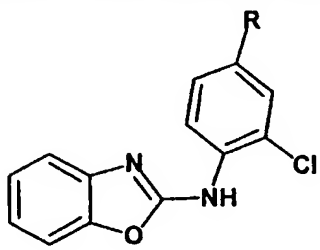
74c 2-chloro-4-methylbenzenesulfonyl chloride. yield 47% as an oil.

for examples 76.9, 79.8 and 351.

^{1}H NMR ($CDCl_3$) δ 8.02 (1H, d, J = 8.8 Hz), 7.46 (1H, s), 7.28 (1H, d, J = 8.8 Hz), 2.47 (3H, s)

EXAMPLE 75

This illustrates the synthesis of compound **75**.



75.1 R=NO2
75 R=NH2

By the method of example 201, 2-chlorobenzoxazole (5 g) and 2-chloro-4-nitroaniline (6.1 g) were coupled to provide nitro compound **75.1** (2.6g) as a yellow solid.

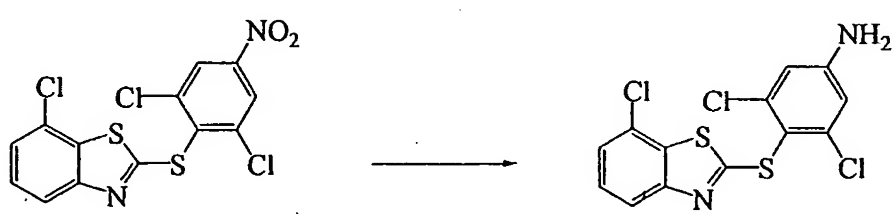
^{1}H NMR (d6-acetone) δ 9.514 (s, 1H), 9.01 (d, J=9 Hz, 1H), 8.4 (s, 1H), 8.37 (dd, J=8.4, 2 Hz, 1H), 7.58 (d, J=8.4 Hz, 1H), 7.52 (d, J=8 Hz, 1H), 7.34 (t, J=7.6 Hz, 1H), 7.28 (t, J= 7.6 Hz, 1H). MS (M-H) 288; (2M-2H+Na) 599.

Reduction by the method of example 32 gave the aniline **75** (93%) as a grey solid.

^{1}H NMR (d6-acetone) δ 8.45 (br s, 1H), 7.796 (d, J=8.4 Hz, 1H), 7.353 (d, J=7.6 Hz, 1H), 7.335)d, J=7.6 Hz, 1H), 7.191 (t, J=7.6 Hz, 1H), 7.088 (t, J=8 Hz, 1H), 6.846 (d, J=2.4 Hz, 1H), 6.673 (dd, J=8.8, 2.4 Hz, 1H), 4.912 (br s, 2H). MS (M+H) 260.1

EXAMPLE 76

This example illustrates the preparation of **76.2** and sulfonamides derived from it.



76.1 **76.2**

3,5-dichloro-4-mercapto nitrobenzene (prepared by the method of Price and Stacy, *J. Amer. Chem. Soc.* 68, 498-500 (1946)) (0.65g) and 2,7-dichlorobenzothiazole (**73.2**) were combined by the method of Example 73, to afford the nitro derivative (**76.1**) as a yellow solid (0.95g).

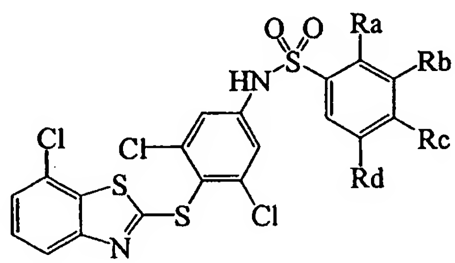
^{1}H NMR (DMSO) δ 8.587 (s, 2H), 7.852 (m, 1H), 7.54 (m 2H). Anal. calcd: 39.87 % C, 1.29 % H, 7.15 % N; found 39.62 %C, 1.21 % H, 7.00 % N.

Reduction of the nitro derivative (**76.1**) (0.92 g) by the method of example 32 gave the aniline (**76.2**) (0.76g) after flash chromatography.

^{1}H NMR (DMSO) δ 7.822 (d, J=8 Hz, 1H) 7.509 (t, J=8Hz, 1H), 7.465 (d, J=6.8 Hz, 1H) 6.882 (s, 2H), 6.529 (br s, 2H). MS (M+H) 361. Anal. calcd: 43.177 % C, 1.95 % H, 7.74 % N; found: 43.10 %C, 2.05 % H, 7.65 % N.

Reaction of the aniline **76.2** according to the method of example 3 with various sulfonyl chlorides gave the sulfonamides of Table 11.

Table 11



	Ra	Rb	Rc	Rd	m/e (M-H)
76.3	Cl	H	CF_3	H	601
76.4	H	H	t-Bu	H	
76.5	Cl	H	Cl	H	567
76.6	Cl	H	H	H	535 (M+H)
76.7	H	H	H	H	
76.8	Cl	H	t-Bu	H	589
76.9	Cl	H	Me	H	547

Example 76.3

^{1}H NMR (DMSO) δ 11.96 (br s, 1H) 8.417 (d, J=8.4 Hz, 1H), 8.209 (s, 2H), 8.013 (d, J=8 Hz, 1H), 7.819 (d, J=6.8 Hz, 1H), 7.514 (m, 2 H), 7.411 (s, 2H). Anal.

calcd: 39.75 % C, 1.50 % H, 4.64 % N; found: 39.48 %C, 1.73 % H, 4.37 % N. MS (M-H) 601.

Example 76.4

Anal. calcd. for M+0.5 H_2O: 48.72 % C, 3.56 % H, 4.94 % N; found: 48.80 %C, 3.68 % H, 4.78 % N.

Example 76.5

^{1}H NMR (DMSO) δ 11.83 (br s, 1H) 8.212 (d, J=8.4 Hz, 1H), 7.962 (d, J=2H, 1H), 7.827 (dd, J=6.8, 2 Hz, 1H), 7.723 (dd, J=8.5, 2.1 Hz, 1H), 7.518 (t, J=7.9 Hz, 1H), 7.492 (dd, J=7.8, 2.0 Hz, 1H), 7.385 (s, 2H). MS (M-H) 567. mp 216°C. Anal. calcd: 39.98% C, 1.59 % H, 4.91 % N; found: 39.81 %C, 1.59 % H, 4.85 % N.

Example 76.6

^{1}H NMR (DMSO) δ 11.72 (br s, 1H), 8.222 (d, J=8 Hz, 1H), 7.822 (dd, J=7.2, 2.0 Hz, 1H), 7.730 (d, J=4 Hz, 2H), 7.636 (m, 1H), 7.516 (t, J=8 Hz, 1H), 7.490 (d, J=8 Hz, 1H), 7.379 (s, 2H). MS (M+H) 535.

Example 76.7

^{1}H NMR (DMSO) δ 11.38 (br s, 1H), 8.906 (d, J=8 Hz, 2H), 7.827 (dd, J=7.2, 2.0 Hz, 1H), 7.721 (t, J=6.8 Hz, 1H), 7.655 (t, J=8 Hz, 2H), 7.519 (t, J=8 Hz, 1H), 7.493 (d, J=6.8 Hz, 1H), 7.412 (s, 2H).

Example 76.8

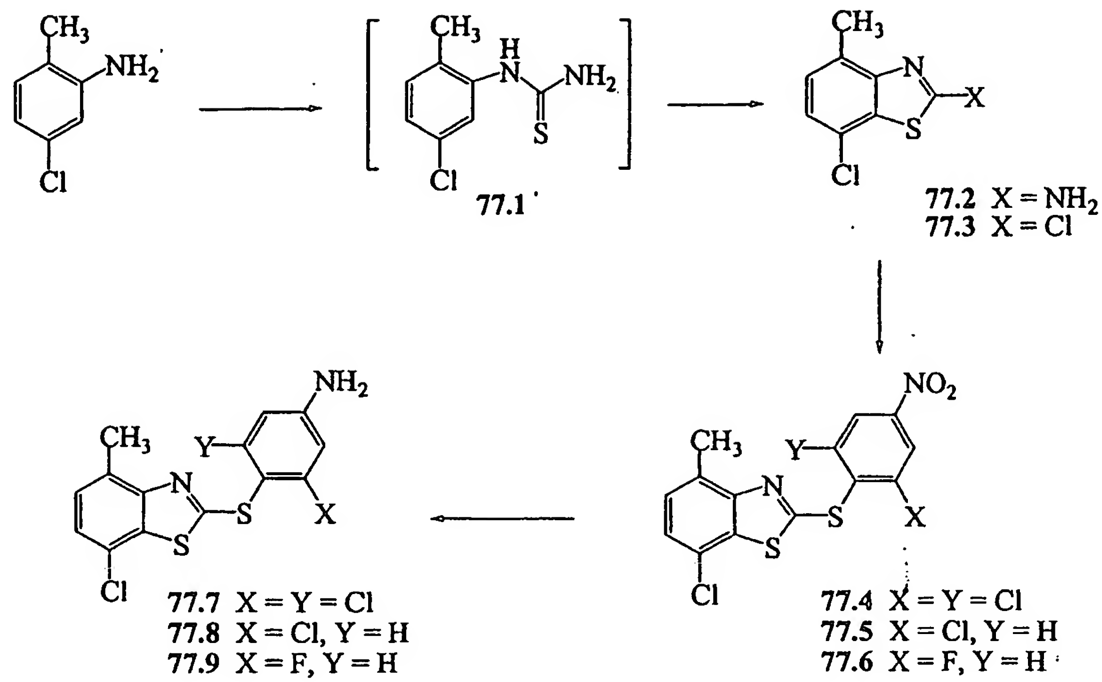
^{1}H NMR (DMSO) δ 11.70 (1H, s), 8.13 (1H, d, 8.4), 7.80-7.87 (1H, m), 7.63-7.71 (2H, m), 7.48-7.55 (2H, m), 7.39 (2H, s). MS (M-H) 589. mp 131.3 °C. Anal. calcd: C 46.63, H 3.06, N 4.73; found C 48.09, H 3.65, N 4.35

Example 76.9

^{1}H NMR (DMSO) δ 11.70 (1H, s), 8.07-8.20 (1H, m), 7.80-7.93 (1H, m), 7.35-7.65 (6H, m). MS (M-H) 546.8. mp 220.9 °C.

EXAMPLE 77

This example illustrates the preparation of anilines 77.7, 77.8 and 77.9



77.1

77.2 X = NH_2
77.3 X = Cl

77.4 X = Y = Cl
77.5 X = Cl, Y = H
77.6 X = F, Y = H

77.7 X = Y = Cl
77.8 X = Cl, Y = H
77.9 X = F, Y = H

In analogy to the procedures of Weinstock et. al (*J. Med. Chem.* **30**:1166-1176 (1987), conc. sulfuric acid (8.74 g) was added slowly to a solution of 5-chloro-2-methylaniline (25g) in chlorobenzene (120 mL) to form a thick slurry. Powdered NaSCN (18.6g) was added. The mixture was heated at 110°C for one hour then maintained at 50°C overnight. After dilution with hexane (300 mL), the solid was collected by filtration, washed with hot water and rinsed with ethyl ether to afford 15.65g of intermediate thiourea **77.1** which was used directly in the next step.

Preparation of 2-amino-4-methyl-7-chlorobenzothiazole (**77.2**).

Bromine (25.44g) was added to a suspension of **77.1** (15g) in chloroform (110 mL) maintained below +10°C. After the addition was complete, the reaction was allowed to warm to RT then heated at reflux for 30 minutes. After cooling, the orange solid was collected by filtration and suspended in acetone (100mL) which discharges the remaining color. Solids were collected by filtration and rinsed with ethyl ether to afford the HBr salt.

^{1}H NMR (DMSO) δ 7.182 (d, J=8 Hz, 1H), 7.137 (d, J=8 Hz, 1H), 2.40 (s, 3H).

The salt was suspended in water at 95°C. The pH of the suspension was adjusted to pH 9 with 0.5 N NaOH. After cooling, the solids were collected by filtration,

rinsed with water and dissolved in ethylether/methylene chloride. The organic layer was dried over magnesium sulfate. After concentration, 2-amino-4-methyl-7-chlorobenzothiazole (77.2) (7.47g) was obtained as a white solid.

MS (M+H) 199. Anal. calcd.: 48.36 % C, 3.55 % H, 14.10 % N; found: 48.29 %C, 3.55 % H, 14.01 % N.

Preparation of 2-7-dichloro-4-methyl-benzothiazole (77.3)

To a slurry of 2-amino-4-methyl-7-chlorobenzothiazole(77.2) (6.37g) in H_3PO_4 (85%, 213 ml) in a 500 ml 3-necked flask with mechanical stirring and an internal temperature of < –10°C, was added dropwise a solution of $NaNO_2$ (6.87g) in water (11 ml). The mixture was warmed to 0° for 30 minutes and then recooled. The slurry was then slowly added to a cold (~-5°C) solution of CuSO4•5 H_2O (32 g) and NaCl (40g) in water (128 ml) with vigorous mechanical stirring. After the foaming subsides and warming to RT, the solids were collected by filtration and rinsed with water. The solids were dissolved in ether leaving some insoluble residue. The ether solution was washed with water, and sodium bicarbonate solution. After the organic layer was concentrated, the residue was purified by flash chromatography with 10% methylene chloride in hexane to afford 2-chloro-4-methyl-7-chlorobenzothiazole (77.3) (4.48g).

^{1}H NMR ($CDCl_3$) δ 7.288 (d, J=8 Hz, 1H), 7.231 (dq, J=8. 0.8 Hz, 1H), 2.651 (d, J=0.8Hz, 3H). Anal. calcd.: 44.06 % C, 2.31 % H, 6.42 % N; found: 44.16 %C, 2.34 % H, 6.32 % N.

Coupling of 77.3 (0.65 g) with 3,5-dichloro-4-mercapto nitrobenzene by the method of example 73 gave after flash chromatography the nitro derivative **77.4** (0.97g) as a yellow solid.

^{1}H NMR (DMSO) δ 8.394 (s, 2H), 7.237 (d, J=8 Hz, 1H), 7.209 (d, J=8 Hz, 1H), 2.621 (s, 3H). MS (M+H) 405

Coupling of 77.3 (0.7 g) with 3-chloro-4-mercapto nitrobenzene by the method of example 73 gave the nitro derivative **77.5** (1.02 g) as a yellow solid.

^{1}H NMR (DMSO) δ 8.535 (br s, 1H), 8.261 (dd, J= 8.4, 2 Hz, 1H), 8.040 (d, J=8.4 Hz, 1H), 7.496 (d, J=8.4 Hz, 1H), 7.419 (d, J=8.4 Hz, 1H), 2.601 (s, 3H). MS (M+H) 371. Anal. calcd.: 45.40 % C, 2.18 % H, 7.57 % N; found: 45.25 %C, 2.23 % H, 7.49 % N.

Coupling of **77.3** (1.12 g) with 3-fluoro-4-mercapto nitrobenzene by the method of example 73 gave after flash chromatography the nitro derivative **77.6** (SY1904-2) (1.8 g) ^{1}H NMR

Reduction of **77.4** (0.96g) with tin dichloride by the method of example 32 gave the aniline **(77.7)** (0.84g) used directly in later reactions:

^{1}H NMR (DMSO) δ 7.352 (d, J=8 Hz, 1H), 7.322 (d, J=8 Hz, 1H), 6.884 (s, 2H), 6.533 (br s, 2H), 2.565 (s, 3H).

Reduction of **77.5** (1.13 g) with tin dichloride by the method of example 32 gave the aniline **(77.8)** (1.04 g) used directly in later reactions:

^{1}H NMR (DMSO) δ 7.543 (d, J=8.4 Hz, 1H), 7.329 (d, J=8 Hz, 1H), 7.301 (d, J=8 Hz, 1H), 6.889 (d, J=2 Hz, 1H), 6.663 (dd, J= 8.4, 2.4Hz, 1H), 6.231 (br s, 2H), 2.557 (s, 3H). MS (M+H) 341. Anal. calcd. for M+0.25 H_2O: 48.63 % C, 3.06 % H, 8.10 % N; found: 48.67 %C, 3.06 % H, 7.96 % N.

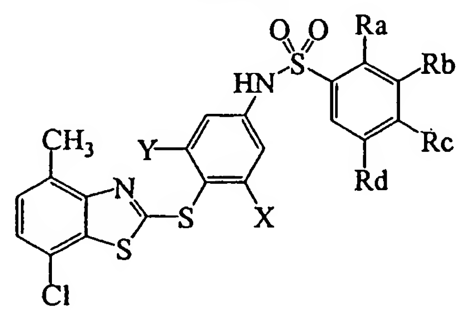
Reduction of **77.6** (1.75 g) with tin dichloride by the method of example 32 gave after chromatography the aniline **(77.9)** (1.2 g)

^{1}H NMR: δ 7.43 (1H, t, 8.3), 7.30-7.37 (2H, m), 6.53-6.58 (2H, m), 6.28 (2H, s).

EXAMPLE 78

Treatment of the anilines **77.7**, **77.8** or **77.9** by the method of example 3 with various sulfonyl chlorides gave the sulfonamides of **Table 12.**

Table 12



	X	Y	Ra	Rb	Rc	Rd	m/e (M-H)
78.1	Cl	Cl	Cl	H	Cl	H	581
78.2	Cl	Cl	Cl	H	CF_3	H	615
78.3	Cl	Cl	Cl	H	Cl	Me	595
78.4	Cl	H	Cl	H	CF_3	H	581

78.5	Cl	H	Cl	H	Cl	H	565
78.6	F	H	Cl	H	CF_3	H	565
78.7	F	H	Cl	H	Cl	H	531

Example **78.1**

^{1}H NMR (DMSO) δ 11.813 (br s, 1H), 8.208 (d, J=8.8 Hz, 1H), 7.951 (d, J=2 Hz, 1H), 7.716 (dd, J=8.4, 2 Hz, 1H), 7.396 (s, 2H), 7.377 (d, J=8.4 Hz, 1H), 7.334 (d, J=8 Hz, 1H), 2.516 (s, 3H). MS (M-H) 581. Anal. calcd.: for M+ H_2O: 39.85 % C, 2.17 % H, 4.65 % N; found: 40.10 %C, 1.89 % H, 4.57 % N.

Example **78.2**

^{1}H NMR (DMSO) δ 11.975 (br s, 1H), 8.416 (d, J=8.4 Hz, 1H), 8.205 (br s, 1H), 8.012 (d, J=8 Hz, 1H), 7.423 (s, 2H), 7.376 (d, J=8 Hz, 1H), 7.332 (d, J=8 Hz, 1H), 2.512 (s, 3H). MS (M-H) 615. Anal. calcd.: 40.79 % C, 1.79 % H, 4.53 % N; found: 41.05 %C, 1.86 % H, 4.57 % N.

Example **78.3**

^{1}H NMR (DMSO) δ 11.748 (s, 1H), 8.233 (s, 1H), 7.880 (s, 1H), 7.407 (s, 2H), 7.370 (d, J=8 HZ, 1H), 7.330 (d, J=8 Hz, 1H), 2.408 (s, 3H). MS (M-H) 595. Anal. calcd.: 42.12 % C, 2.19 % H, 4.68 % N; found: 41.84 %C, 2.23 % H, 4.51 % N.

Example **78.4**

^{1}H NMR (DMSO) δ 11.73 (1H, s), 8.38 (1H, d, J = 8.3 Hz), 8.19 (1H, s), 7.99 (1H, d, J = 8.3 Hz), 7.88 (1H, d, J = 8.6 Hz), 7.45 (1H, d, J = 2.3 Hz), 7.23-7.40 (3H, m). MS (M-H) 580.8 (M-H). mp 189.0 °C.

Example **78.5**

^{1}H NMR (DMSO) δ 11.57 (1H, s), 8.17 (1H, d, J = 8.6 Hz), 7.92 (1H, d, J = 2.1 Hz), 7.78 (1H, d, J = 8.5 Hz), 7.69 (1H, dd, J = 8.6, 2.1 Hz), 7.43 (1H, d, J = 2.3 Hz), 7.30-7.38 (2H, m), 7.25 (1H, dd, J = 8.6, 2.4 Hz). MS (M-H) 546.9. mp 218.1 °C.

Example **78.6**

^{1}H NMR: δ 8.04 (1H, d, 8.3), 8.18 (1H, s), 7.99 (1H, d, 8.3), 7.80 (1H, t, 8.3), 7.30-7.40 (2H, m), 7.10-7.22 (2H, m). MS (M-H) 565.0. mp 221.2 °C. Anal. calcd.: C 44.45, H 2.13, N 4.94; found C 44.01, H 2.18, N 4.67.

Example **78.7**

^{1}H NMR (DMSO) δ 11.60 (1H, s), 8.18 (1H, d, 8.6), 7.91 (1H, d, 2.0), 7.79 (1H, t, 8.4), 7.69 (1H, dd, 8.6, 2.1), 7.30-7.40 (2H, m), 7.10-7.20 (2H, m). MS (M-H) 530.9. mp 230.4 °C. Anal. calcd.: C 44.99, H 2.27, N 5.25; found C 44.49, H 2.26, N 5.08.

EXAMPLE 79

This example illustrates the preparation of compounds **79.1** to **79.7.**

To a solution of 5-chloro-2-mercaptobenzothiazole (Acros) (2g), KOH (630 mg) in water (8 mL) at 100° C was added a solution of 3,4-dichloronitrobenzene (1.88g) in n-propanol (24 mL). The mixture was heated at reflux for 72 hrs. After cooling, the solids were collected by filtration and rinsed with water. The solids were dried under vacuum to afford the nitro derivative **79.1** (2.25 g) as a yellow solid used directly in the next step.

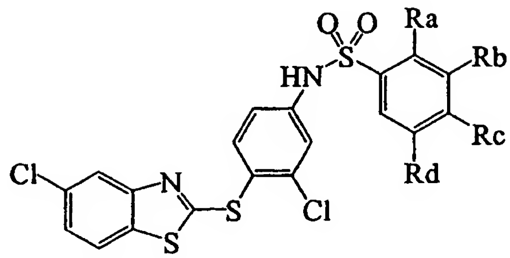
^{1}H NMR (DMSO) δ 8.54 (d, J=2.4 Hz, 1H), 8.26 (dd, J=8.6, 2.4 Hz, 1H), 8.123 (d, J=8.6 Hz1, 1H), 8.08 (d, J=1.9 Hz, 1H), 8.03 (d, J=8.7 Hz, 1H), 7.533 (dd, J=8.6, 2.1).

Reduction of **79.1** (2.2 g) with tin dichloride by the method of example 32 gave after work-up the aniline **(79.2)** (1.2 g) which was used directly in later reactions.

^{1}H NMR (DMSO) δ 7.94 (d, J=8.4 Hz, 1H), 7.891 (d, J=1.6 Hz, 1H), 7.537 (d, J=8.4 Hz, 1H), 7.371 (dd, J=8.4, 2.1 Hz, 1H), 6.877 (d, J=2.4 Hz, 1H), 6.651 (dd, J=8.4, 2.4 Hz, 1H), 6.203 (s, 2H). MS (M+H) 327

Treatment of the aniline **79.2** by the method of example 3 with various sulfonyl chlorides gave the sulfonamides of **Table 13**.

Table 13



	Ra	Rb	Rc	Rd	m/e (M-H)
79.3	Cl	H	Cl	Me	547
79.4	Cl	H	Cl	H	533 (M+H)
79.5	Cl	H	CF_3	H	567
79.6	H	Cl	Cl	H	533
79.7	Me	H	Cl	Me	527

Example 79.3

^{1}H NMR(DMSO) δ 11.52 (1H, s), 8.20 (1H, s), 7.84-8.00 (4H, m), 7.35-7.43 (2H, m), 7.22 (1H, d, J = 8.5 Hz), 2.41 (3H, s). MS (M-H) 546.8. mp 203.7 °C.

Example 79.4

^{1}H NMR(DMSO) δ 11.57 (1H, s), 8.18 (1H, d, J = 8.5 Hz), 7.90-7.98 (2H, m), 7.86 (1H, d, J = 8.5 Hz), 7.72 (1H, d, J = 8.7 Hz), 7.37-7.43 (2H, m), 7.22(1H, d, J = 8.8 Hz). MS (M+H) 532.8. mp 174.7 °C.

Example 79.5

^{1}H NMR(DMSO) δ 8.38 (1H, d, 8.4 Hz), 8.21 (1H, s), 8.01 (1H, d, J = 8.2 Hz), 7.90-7.96 (2H, m), 7.86 (1H, d, J = 7.7 Hz), 7.42 (2H, s), 7.23 (1H, d, J = 8.6 Hz). MS (M-H) 566.9. mp 158.8 °C.

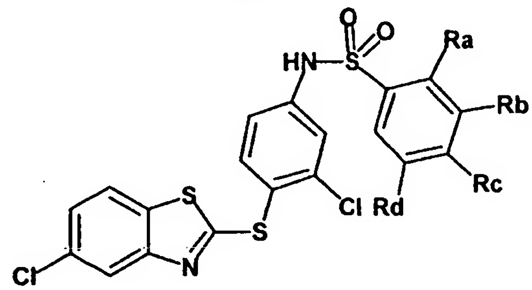
Example 79.6

^{1}H NMR(DMSO) δ 11.25 (1H, s), 8.06 (1H, d, J = 1.5 Hz), 7.80-7.96 (5H, m), 7.40-7.46 (2H, m), 7.27-7.32 (1H, m). MS (M-H) 532.8. mp 201.2 °C.

Example 79.7

^{1}H NMR(DMSO) δ 11.30 (1H, s), 8.00 (1H, s), 7.90-7.98 (2H, m), 7.84 (1H, d, J = 8.6 Hz), 7.57 (1H, s), 7.35-7.44 (2H, m), 7.18-7.23 (1H, m), 2.57 (3H, s), 2.37 (3H, s). mp 205.1 °C.

Table 14



	Ra	Rb	Rc	Rd	m/e (M-H)
79.3	Cl	H	Cl	Me	547
79.4	Cl	H	Cl	H	533 (M+H)
79.5	Cl	H	CF_3	H	567
79.6	H	Cl	Cl	H	533
79.7	Me	H	Cl	Me	527
79.8	Cl	H	Me	H	513
79.9	Cl	H	t-Bu	H	555

Example 79.8

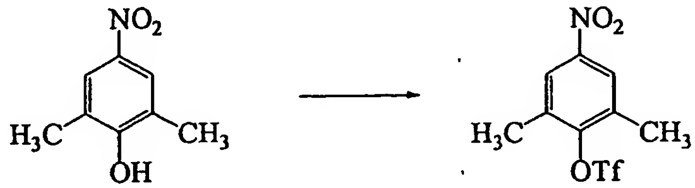
^{1}H NMR (d_6-DMSO) δ 11.43 (1H, s), 8.08 (1H, d, J = 8.0 Hz), 7.90-8.00 (2H, m), 7.85 (1H, d, J = 8.5 Hz), 7.57 (1H, s), 7.37-7.47 (3H, m), 7.21 (1H, d, J = 8.4 Hz), 2.38 (3H, s). MS (M-H) 512.9. mp 201.0 °C. Anal. calcd.: C46.56, H 2.54, N 5.43; found C 46.93, H 2.58, N 5.40.

Example 79.9

^{1}H NMR (d_6-DMSO) δ 11.44 (1H, s), 8.10 (1H, d, J = 8.3 Hz), 7.90-7.97 (2H, m), 7.86 (1H, d, J = 8.6 Hz), 7.60-7.68 (2H, m), 7.37-7.43 (2H, m), 7.23 (1H, dd, J = 8.5, 2.4 Hz), 1.29 (9H, s). MS (M-H) 554.9. mp 177.8 °C. Anal. calcd.: C 49.51, H 3.43, N 5.02; found C 49.67, H 3.44, N 4.97.

EXAMPLE 80

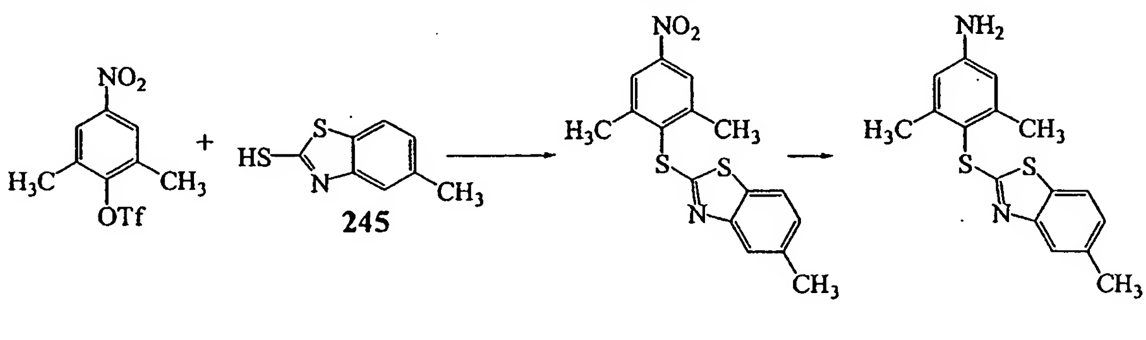
This illustrates the synthesis of compound **80.4**.



80.1

2,6-dimethyl-4-nitro-phenol (4.93 g, 29.5 mmol) was suspended in anhydrous CH_2Cl_2 (30 mL). Hünig's base (12.4 mL, 70 mmol) was added to give a homogeneous, dark red solution. The reaction mixture was cooled to –15 °C and triflic anhydride (10 g, 35 mmol) was slowly added. The very dark reaction mixture was stirred at –15 °C for 15 minutes, then poured into 3N HCl (100 mL). The layers were separated and the aqueous layer was extracted 1 x 150 mL CH_2Cl_2. The combined organic layers were washed 1 x 50 mL sat. brine, dried over $MgSO_4$, and concentrated to a dark red oil. This oil was filtered through a 2 cm plug of silica gel (eluting with 3:1 hexanes:ethyl acetate) and concentrated to an orange oil which was diluted with 10 mL of hexanes and allowed to stand at room temperature until crystallization of the product took place. The crystals were collected and dried under vacuum. The mother liquor was concentrated, then diluted with 5 mL of CH_2Cl_2 and 25 mL of hexanes and again allowed to stand until crystallization was complete. The second crop was collected by filtration and dried under vacuum. Combined yield of the two crops was 7.87 g of triflate **80.1**.

^{1}H NMR ($CDCl_3$) δ 8.03 (s, 2H); 2.50 (s, 6H).



80.1 **80.2** **80.3**

5-methyl-2-mercaptobenzothiazole (1.45 g, 8 mmol) was suspended in anhydrous THF (3.5 mL). A solution of potassium *tert*-butoxide (7.35 mL, 1.0 N in THF) was added in one portion. The very thick precipitate of the mercaptobenzothiazole potassium salt was dissolved by addition of DMF (1 mL). Triflate **80.1** (2 g, 6.7 mmol)

was dissolved in DMF (1 mL) and added to the reaction mixture which was then heated to 50 °C for 16 h. The reaction mixture was pouted into 100 mL DI water and extracted 2 x 50 mL of ethyl acetate. The combined organic layers were washed with sat. brine, dried over $MgSO_4$, filtered, concentrated, and the residue purified by flash chromatography (silica gel, 19:1 to 4:1 hexanes:ethyl acetate). Fractions containing the desired product were concentrated and the residue recrystallized from hot hexanes:ethyl acetetate. Filtration and drying provided the S-arylated compound **80.2** as bright yellow crystals (0.90 g).

^{1}H NMR (CD_3CN) δ 8.12 (s, 2H); 7.68 (d, 1H); 7.61 (s, 1H); 7.17 (d, 1H); 2.60 (s, 6H); 2.42 (s, 3H). MS (M+H) 331.1

Reduction of **80.2** (0.88 g) by the method of Example 32 gave aniline **80.3** (0.4 g) as a solid.

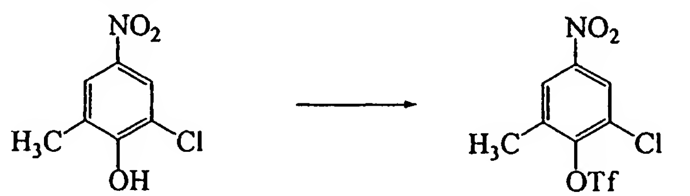
^{1}H NMR ($CDCl_3$) δ 7.723 (m, 1H), 7.598 (s, 1H), 7.122 (d, J=8.4Hz, 1H), 6.706 (s, 2H), 5.304 (br, 2H), 2.399 (s, 3H), 2.338 (s, 6H)

Sulfonylation of **80.3** (400 mg) by the method of example 3 gave **80.4** (Table 15)(0.36 g).

^{1}H NMR (DMSO) δ 11.284 (s, 1H), 8.369 (d, J=8.2Hz, 1H), 8.170 (s, 1H), 7.969 (d, J=8.2 Hz, 1H), 7.676 (d, J=8.2 Hz, 1H), 7.591 (s, 1H), 7.126 (d, J=8.2Hz, 1H), 7.056 (s, 2H), 2.372 (s, 3H), 2.326 (s, 6H). MS (M+H) 543

EXAMPLE 81

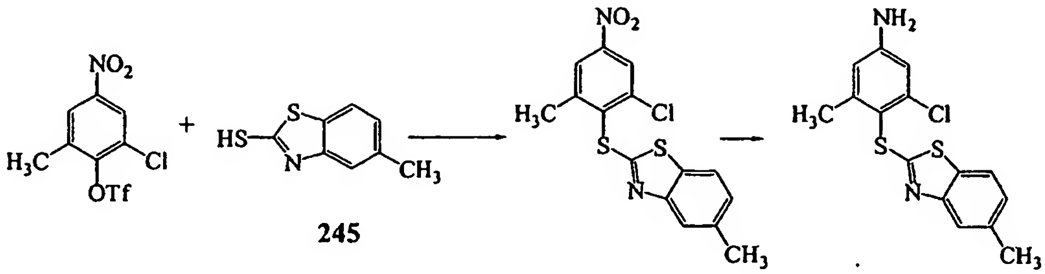
This illustrates the synthesis of compound **81.4**.



81.1

2-chloro-6-methyl-4-nitro-phenol (2.5 g, 13.3 mmol) was converted to triflate **81.1** according to the method given in Example **80**. Triflate **81.1** was an oil and could not be recrystallized. 4.0 g of triflate **81.1** was obtained.

^{1}H NMR (CD_3CN) δ 8.24 (d, 1H); 8.77 (d, 1H); 2.56 (s, 3H).



81.1 81.2 81.3

5-methyl-2-mercaptobenzothiazole (1.36 g, 7.5 mmol) and triflate **81.1** (2 g, 6.26 mmol) were reacted according to the procedure given in Example **80**. S-arylated compound **81.2** was obtained as bright yellow crystals (1.2 g). This product contained a minor amount of a contaminant of unknown structure. This contaminant had no effect on subsequent reactions, nor was it found in subsequent products.

^{1}H NMR (CD_3CN) δ 8.28 (d, 1H); 8.14 (d, 1H); 7.67 (s, 1H); 7.56 (d, 1H); 7.14 (d, 1H); 2.68 (s, 3H); 2.45 (s, 3H). MS (M+H) 351.

Reduction of **81.2** (0.88 g) by the method of Example 32 gave aniline **81.3** (0.4 g) as a solid.

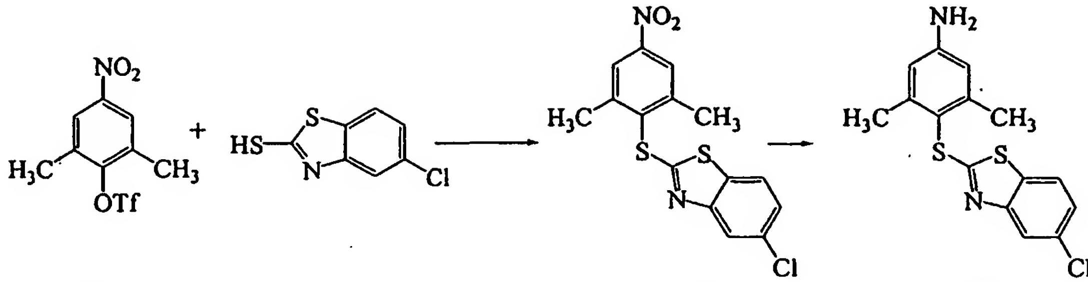
^{1}H NMR (DMSO) δ 7.740 (d, J=8 Hz, 1H), 7.608 (s, 1H), 7.131 (d, J=8 Hz, 1H), 6.732 (d, J=2.6 Hz, 1H), 6.588 (d, J=2.6 Hz, 1H), 6.048 (s, 2H), 2.403 (s, 3H), 2.334 (s, 3H).

Sulfonylation of **81.3** by the method of example 3 gave **81.4** (see **Table 15**).

^{1}H NMR (DMSO) δ 11.610 (s, 1H), 8.398 (d, J=8.4 Hz, 1H), 8.210 (s, 1H), 8.005 (d, J=8.4Hz, 1H), 7.730 (d, J=8Hz 1H), 7.621 (s, 1H), 7.7.276 (d, J=2.8Hz, 1H), 7.167 (m, 2H), 2.409 (s, 3H), 2.397 (s, 3H).

EXAMPLE 82

This illustrates the synthesis of compound **82.3**.



80.1 82.1 82.2

5-chloro-2-mercaptobenzothiazole (202 mg, 1 mmol) and triflate **80.1** (270 mg, 0.9 mmol) were reacted according to the procedure given in Example **80**. S-arylated compound **82.1** was obtained as a light yellow solid (203 mg).

^{1}H NMR (CDCl$_3$) δ 8.09 (s, 2H); 7.83 (d, 1H); 7.56 (d, 1H); 7.26 (dd, 1H); 2.63 (s, 3H). MS (M+H) 351.0

Reduction of **82.1** (0.7 g) by the method of example 32 gave aniline **82.2** (0.62 g).

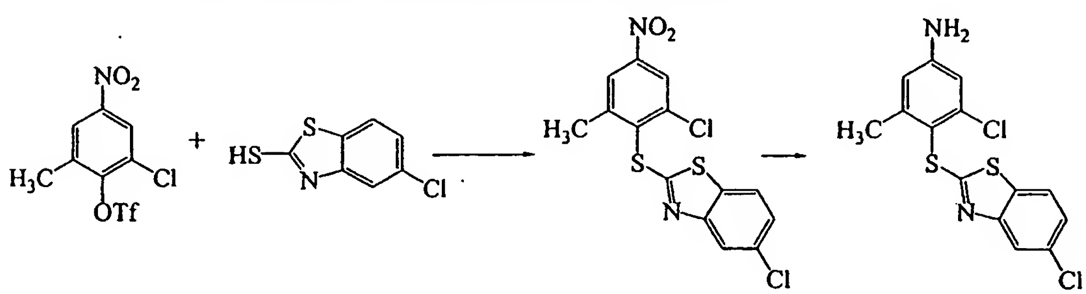
^{1}H NMR (DMSO) δ 7.884 (d, J=8.4 Hz, 1H), 7.846 (d, J=2 Hz, 1H), 7.329 (dd, J=8.4, 2 Hz, 1H), 6.495 (s, 2H), 5.669 (s, 2H), 2.283 (s, 3H). MS (M+H) 321

Sulfonylation of **82.2** by the method of example 3 gave **82.3** (see **Table 15**).

^{1}H NMR (DMSO) δ 11.304 (s, 1H), 8.377 (d, J=8 Hz, 1H), 8.180 (d, J=1.2 Hz, 1H), 7.980 (br d, J=8.4, 1H), 7.874 (d, J=2.4 Hz, 1H), 7.866 (d, J=8 Hz, 1H), 7.365 (dd, J=8.4, 2 Hz, 1H), 7.068 (br s, 2H), 2.341 (s, 3H). MS (M-H) 561

EXAMPLE 83

This illustrates the synthesis of compound **83.3**.



81.1 83.1 83.2

5-chloro-2-mercaptobenzothiazole (0.76 g, 3.75 mmol) and triflate **81.1** (1.0 g, 3.44 mmol) were reacted according to the procedure given in Example **80**. S-arylated compound **83.1** was obtained as a light yellow solid (0.83 g).

^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1H); 8.17 (s, 1H); 7.85 (s, 1H); 7.61 (d, 1H); 7.30 (d, 1H); 2.71 (s, 3H). MS (M+H) 371

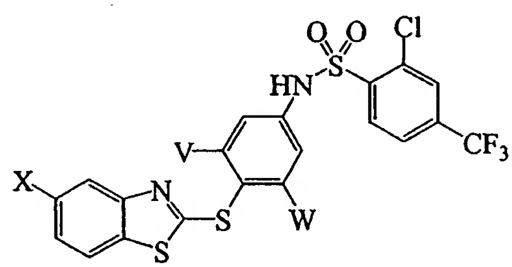
Reduction of **83.1** (0.8 g) by the method of Example 32 gave aniline **83.2** (0.47 g).

^{1}H NMR (DMSO) δ 7.918 (d, J=8.8 Hz, 1H), 7.874 (d, J=2 Hz, 1H), 7.356 (dd, J=8.4, 2 Hz, 1H), 6.745 (d, J=2.4 Hz, 1H), 6.600 (d, J=2 Hz, 1H), 6.089 (br s, 2H), 2.336 (s, 3H). MS (M+H) 341.

Sulfonylation of **83.2** by the method of example 3 gave **83.3** (see Table 15).

^{1}H NMR (DMSO) δ 11.647 (s, 1H), 8.407 (d, J=8.4 Hz, 1H), 8.213 (br s, 1H), 8.008 (br d, J=8.4, 1H), 7.910 (d, J=8 Hz, 1H), 7.90 (s, 1H), 7.396 (d, J=8.8 H, 1H), 7.290 (br s, 1H), 7.188 (br s, 1H), 2.416 (s, 3H). MS (M-H) 581.

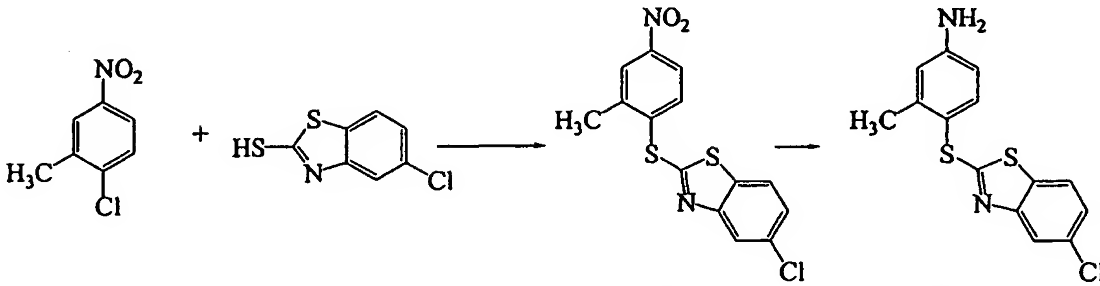
Table 15



	X	V	W	m/e (M-H)
80.4	Me	Me	Me	543 (M+H)
81.4	Me	Me	Cl	
82.3	Cl	Me	Me	561
83.3	Cl	Me	Cl	581
84.3	Cl	H	Me	547

EXAMPLE 84

This illustrates the synthesis of compound **84.3**



84.1 84.2

Sodium hydride (1g, 60% in oil) was added to a solution of 5-chloro-2-mercaptobenzothiazole (5.4 g) in DMF (50 mL). After gas evolution had subsided a solution of 2-chloro-5-nitro toluene in DMF was added and the mixture heated at 60°C for 2 days. After cooling, the solution was filtered. The filtrate was diluted with water and extracted into ethyl ether. The organic layer was concentrated to a brown oil which was treated with hexane to form a solid precipitate which was collected by filtration as **84.1** (0.624 g).

^{1}H NMR (DMSO) δ 8.372 (d, J=2.4 Hz, 1H), 8.171 (dd, J=8.8, 2.4 Hz, 1H), 8.027 (d, J=8.8 Hz, 1H), 8.003 (d, J=8 Hz, 1H), 7.988 (d, J=2 Hx, 1H), 7.454 (dd, J=8.4, 1.6 Hz, 1H), 2.553 (s, 3H).

Reduction of **84.1** (0.6 g) with SnCl2 by the method of example 32 gave after chromatography **84.2** (0.48 g) as a solid.

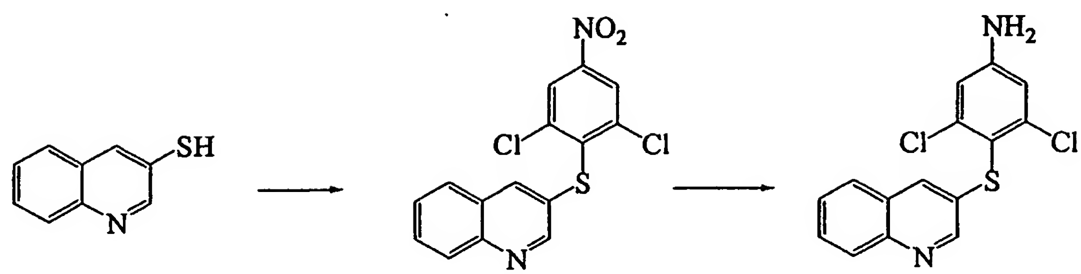
^{1}H NMR (DMSO) δ 7.899 (d, J=8.8 Hz, 1H), 7.853 (d, J=2 Hz, 1H), 7.345 (d, J=8.4 Hz, 1H), 7.336 (dd, J=8.4, 2 Hz, 1H), 6.631 (d, J=2 Hz, 1H), 6.531 (dd, J=8.4, 2 Hz, 1H), 5.766 (br s, 2H). MS (M+Na) 329

Sulfonylation of **84.2** (0.4 g) by the method of example 3 gave **84.3** (Table 15) (0.66 g) as a foam.

^{1}H NMR (DMSO) δ 11.376 (s, 1H), 8.355 (d, J=8 Hz, 1H), 8.180 (d, J=1.2 Hz, 1H), 7.983 (dd, J=8.4, 2 Hz, 1H), 7.893 (d, J=9.2 Hz, 1H), 7.88 (s, 1H), 7.656 (d, J=8.4 H, 1H), 7.377 (dd, J=8.8, 1.6 Hz, 1H), 7.211 (d, J=2.8 Hz, 1H), 7.108 (dd, J=8.4, 2 Hz, 1H), 2.334 (s, 3H). MS (M-H) 547

EXAMPLE 85

This illustrates the synthesis of compound **85.3**



85.1 85.2 85.3

Compound **85.1** was prepared by a modification of the published procedure of Albert and Barlin (J. Chem. Soc. 2384-2396 (1959). 3-Aminoquinoline (15.0 g, 105 mmol) was suspended in a mixture of 10N HCl (40 mL), ice (21g) and water (100 mL) at 0-5 °C, before sodium nitrite (7.6 g, 110 mmol) was added slowly. The mixture was then added portionwise to another solution of potassium ethyl xanthate (20.8 g, 125 mmol) in water (60 mL) at 45 °C. The mixture was heated for 1 hr before cooling off. The mixture was then extracted with ether. The ethereal solution was washed with 2N NaOH solution, water, and brine before drying over magnesium sulfate. After filtration, the removal of the solvent gave a brown oil (15g), which was then dissolved in ethanol (150 mL) and refluxed with KOH (25g) under nitrogen overnight. The ethanol solvent was then removed under vacuum, and the residue was separated between water and ether. The ethereal solution was discarded. The aqueous solution was acidified to pH = ~4, before it was extracted with ether. Then ethereal solution was washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum to give crude product (7.5g) as a brown oil. Subsequent flash chromatography with eluent (0%-5%-10% ethyl acetate / dichloromethane) produced 3-mercaptoquinoline (**85.1**) (5.35g, 32% yield) as a solid.

^{1}H NMR (DMSO) δ 9.02 (1H, d, J = 2.3 Hz), 8.63 (1H, d, J = 2.2 Hz), 7.95-8.05 (2H, m), 7.75-8.02 (1H, m), 7.60-7.67 (1H, m).

To a mixture of 3-mercaptoquinoline (**85.1**)(1.18 g, 7.33 mmol) and 1,2,3-chloro-5-nitrobenzene (1.66 g, 7.33 mmol) dissolved in ethanol (100 mL), was added a THF solution of t-BuOK (7.5 mL, 1M). The mixture was then heated at 80 °C overnight before cooling off. After the removal of ethanol solvent, the mixture was separated between ethyl acetate and water. The organic solution was washed with brine, dried over magnesium sulfate and filtered. The filtrate was then concentrated to give a crude

product, which was then flash chromatographed with eluent (10% hexanes / dichloromethane) to afford **85.2** (1.80 g, 70% yield) as a yellow oil.

^{1}H NMR (DMSO) δ 8.75 (1H, d, J = 2.3), 8.51 (1H, s), 8.22 (1H, s), 8.01 (1H, d, J = 8.4 Hz), 7.92 (1H, d, J = 7.6 Hz), 7.74-7.80 (1H, m), 7.60-7.66 (1H, m).

An ethyl acetate solution (100 mL) of **85.2** (1.80 g, 5.1 mmol) and tin chloride (II) dihydrate (6.88 g, 30 mmol) was heated at reflux overnight before cooling off. The solution was then poured into 1N NaOH solution (400 mL). After stirring for 30 min, the mixture was separated, and the organic solution was washed with water, saturated sodium bicarbonate and brine. After drying over magnesium sulfate, the solution was filtered and concentrated under vacuum. The residue was mixed with dichloromethane (10 mL) and sonicated. Subsequent vacuum filtration provided the aniline **85.3** (1.35g, 82% yield) as an off-white solid.

^{1}H NMR (DMSO) δ 8.61 (1H, d, J = 2.4), 7.96 (1H, d, J = 8.4 Hz), 7.88 (1H, d, J = 8.2 Hz), 7.83 (1H, d, J = 2.2 Hz), 7.67-7.72 (1H, m), 7.54-7.60 (1H, m). mp 213.2 °C.

EXAMPLE 86

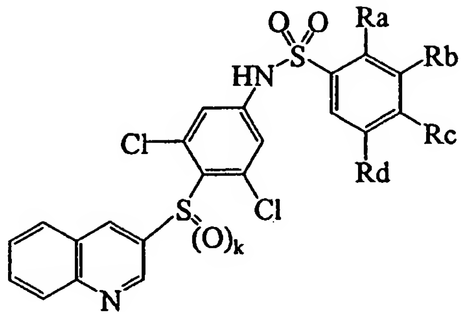
This illustrates the synthesis of compound **86** (see Table 16).

The aniline **85.3** (250 mg, 0.78 mmol) and 2-chlorobenzenesufonyl chloride (339 mg, 1.60 mmol) were dissolved in a mixed solvent of THF (5 mL) and dichloromethane (5 mL). To the solution was added pyridine (0.185 mL, 2.34 mmol) and catalytic amount of DMAP. The solution was heated at 50 °C to distill off dichloromethane, and then THF with assistance of vacuum. The residue was flash chromatographed with eluent (2.5% ethyl acetate / dichloromethane) to give sulfonamide **86** (302 mg, 78%) as an off-white solid.

^{1}H NMR(DMSO) δ 11.58 (1H, s), 8.61 (1H, d, J = 2.4 Hz), 8.19 (1H, d, J = 7.6 Hz), 7.83-8.00 (3H, m), 7.67-7.75 (3H, m), 7.56-7.65 (2H, m), 7.31 (2H, s). MS (M+H) 494.9. mp: 219.6 °C. Anal. calcd: C 50.87, H 2.64, N 5.65; found C 50.86, H 2.62, N 5.52.

The compounds of Table 16 were prepared by the method of example **86** from compound **84.3** and the corresponding arylsulfonyl chloride.

Table 16



	k	R_a	R_b	R_c	R_d	m/e (M+H)
86	0	Cl	H	H	H	495
87.1	0	Cl	H	Cl	H	529
87.2	0	H	H	H	H	461
87.3	0	Cl	H	CF_3	H	561 (M-H)
88.1	1	Cl	H	H	H	511
88.2	1	Cl	H	Cl	H	543 (M-H)
88.3	1	H	H	H	H	477

EXAMPLE 87

Example **87.1**

^{1}H NMR(DMSO) δ 11.66 (1H, broad), 8.63 (1H, d, J = 2.3 Hz), 8.18 (1H, d, J = 8.6 Hz), 7.85-8.00 (4H, m), 7.70-7.75 (2H, m), 7.57-7.62 (1H, m), 7.32 (2H, s). MS (M+H) 529.0. mp 214.0 °C. Elemental Analysis: theory C 47.56, H 2.28, N 5.28; found C47.30, H 2.36, N 5.37.

Example **87.2**

^{1}H NMR(DMSO): δ 11.22 (1H, s), 8.61 (1H, d, J = 2.3 Hz), 7.82-7.98 (5H, m), 7.57-7.75 (5H, m), 7.34 (2H, s). MS (M+H) 461.0. mp 246.8 °C. Elemental Analysis theory C 54.67, H 3.06, N 6.07; found C 54.71, H 3.05, N 5.94.

Example **87.3**

^{1}H NMR (DMSO) δ 11.70-12.00 (1H, broad), 8.60-8.67 (1H, m), 8.35-8.43 (1H, m), 8.20-8.25 (1H, m), 7.56-8.06 (6H, m), 7.32-7.38 (2H, m). MS (M-H) 560.9. mp: 225.1 °C. Elemental Analysis: theory C 46.86, H 2.15, N 4.97; found C. 47.01, H 2.26, N 4.98.

EXAMPLE 88

General procedure for sulfur oxidation to the sulfoxide:

A naphthylthioether of examples 86 or 87 (0.2 mmol) was dissolved in a mixed solvent of dichloromethane (10 mL) and methanol (5 mL). To the solution was added mCPBA (120 mg, 0.7 mmol, 77% pure) in six batches over 20 minute intervals. Then the solution was washed with 5% sodium thiosulfate solution, 1% sodium bicarbonate solution and brine and then dried over magnesium sulfate. After filtering, the filtrate was concentrated to give a crude product, which was then flash chromatographed with eluent (5%-30% ethyl acetate / dichloromethane) to afford the corresponding sulfoxide.

Example **88.1**

^{1}H NMR (DMSO): δ 11.75 (1H, s), 8.82 (1H, s), 8.68 (1H, s), 8.15-8.20 (2H, m), 8.09 (1H, d, J = 8.5 Hz), 7.85-7.91 (1H, m), 7.67-7.75 (3H, m), 7.57-7.64 (1H, m), 7.17 (2H, s). MS (M+H) 511. mp 239.5 °C with decomposition. Elemental Analysis: theory C 49.28, H 2.56, N 5.47; found C 49.30, H 2.63, N 5.37.

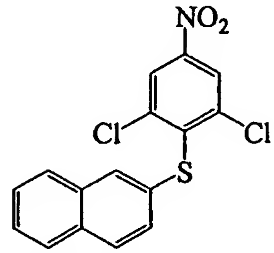
Example **88.2**

^{1}H NMR(DMSO): δ 11.5-12.0 (broad), 8.83 (1H, s), 8.68 (1H, s), 8.15-8.20 (2H, m), 8.09 (1H, d, J = 8.5 Hz), 7.85-7.92 (2H, m), 7.55-7.75 (2H, m), 7.17 (2H, s). MS (M-H) 542.9. mp: 234.4. Elemental Analysis: theory C 46.17, H 2.21, N 5.13; found C 45.97, H 2.26, N 4.92.

Example **88.3**

^{1}H NMR(DMSO) δ 11.43 (1H, s), 8.81 (1H, s), 8.68 (1H, s), 8.18 (1H, d, J = 8.2 Hz), 8.09 (1H, d, J = 8.5 Hz), 7.82-7.90 (3H, m), 7.58-7.74 (4H, m), 7.21 (2H, s). MS (M+H) 476.9. mp 261.8 °C with decomposition. Elemental Analysis: theory C 52.83, H 2.96, N 5.87; found C 52.71, H 3.05, N 5.71.

EXAMPLE 89

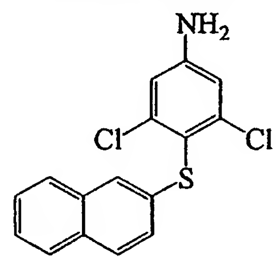


2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-napthalene (89)

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-napthalene was synthesized (100%) from 3,4,5-trichloronitrobenzene (Acros) and napthalene-2-thiol (Avocado) in a similar manner as described in example 1 using DMSO as solvent instead of DMF.

^{1}H NMR (DMSO-d_6) δ 8.48 (s, 2H), 7.95-7.85 (m, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.85-7.8 (m, 1H), 7.75 (d, J = 1.8 Hz, 1H), 7.55-7.45 (m, 2H), 7.25 (dd, J = 8.7, 2.0 Hz, 1H).

EXAMPLE 90

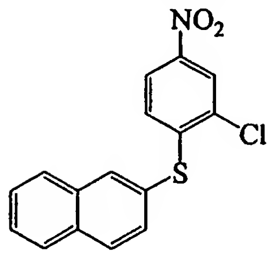


3,5-dichloro-4-(napthalen-2-ylsulfanyl)-phenylamine (90)

To a 0.1M solution 2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-napthalene (89) (774 mg, 2.2 mmol), in EtOAc was added tin(II)chloride dihydrate, obtained from Aldrich, (2.49 g, 11.05 mmol). The resulting mixture was refluxed for 2 hour. The crude reaction mixture was cooled to ambient temperature and excess 2M aqueous NaOH was added and allowed to stir for 15 minutes. Solid tin salts precipitated from the solution, were filtered off through a pad of celite and washed with EtOAc (200 mL). The organic layer was washed twice with brine (200 mL), dried over Na_2SO_4, and concentrated under vacuum to yield 592 mg (84%) of (90) which was used without further purification.

^{1}H NMR (DMSO-d_6) δ 7.88-7.82 (m, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.5-7.4 (m, 3H), 7.13 (dd, J = 8.7, 1.9 Hz, 1H), 6.83 (s, 2H), 6.21 (s, 2H). MS (M-H) 318.

EXAMPLE 91

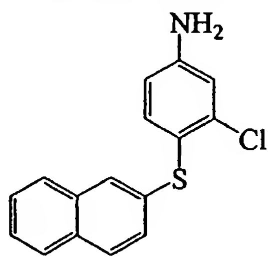


2-(2-Chloro-4-nitro-phenylsulfanyl)-napthalene (91)

2-(2-Chloro-4-nitro-phenylsulfanyl)-napthalene was synthesized (100%) from 3-chloro-4-fluoro-nitrobenzene (Aldrich) and napthalene-2-thiol (Avocado) in a similar manner as described in example 89.

^{1}H NMR (DMSO-d_6) δ 8.4-8.34 (m, 2H), 8.14 (d, J = 8.6 Hz, 1H), 8.09-8.0 (m, 3H), 7.72-7.6 (m, 3H), 6.88 (d, J = 8.9 Hz, 1H).

EXAMPLE 92

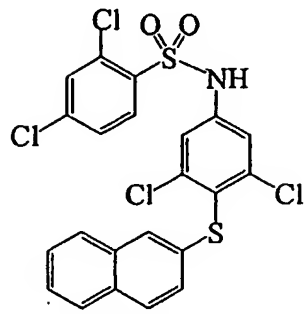


3-chloro-4-(napthalen-2-ylsulfanyl)-phenylamine

3-chloro-4-(napthalen-2-ylsulfanyl)-phenylamine (92) was synthesized (97%) from 2-(2-Chloro-4-nitro-phenylsulfanyl)-napthalene (91) in a similar manner as described in example 90.

^{1}H NMR (DMSO-d_6) δ 7.88-7.8 (m, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.5-7.42 (m, 3H), 7.35 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.6, 1.8 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.6 (dd, J = 8.4, 2.4 Hz, 1H). MS (M+H) 286

EXAMPLE 93

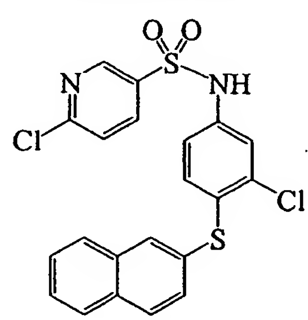


2,4-Dichloro-N-[3,5-dichloro-4-(napthalen-2-ylsulfanyl)-phenyl]-benzenesulfonamide (93)

To a 0.4M solution of 3,5-dichloro-4-(napthalen-2-ylsulfanyl)-phenylamine (90)(153 mg, 0.48 mmol) in THF was added pyridine, obtained from aldrich, (0.19 mL, 2.4 mmol) followed by 2,4-dichlorobenzenesulfonyl chloride, obtained from Maybridge, (129 mg, 0.53 mmol). The resulting mixture was stirred for 6 days. A 1M aqueous solution of HCl (20 mL) was added and the crude reaction mixture was extracted 3x with EtOAc (20 mL). The organic layers were combined and washed once with a brine solution (20 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was chromatographed (5-15% EtOAc in hexane) to yield 125 mg (49%) of 93 as an off white solid.

^1H NMR (DMSO-d_6) δ 11.6 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.88-7.83 (m, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.76-7.73 (m, 1H), 7.1 (dd, J = 8.6, 2.1 Hz, 1H), 7.52-7.44 (m, 3H), 7.32 (s, 2H), 7.21 (s, 2H), 7.1 (dd, J = 8.6, 2.0 Hz, 1H). MS (M-H) 526

EXAMPLE 94

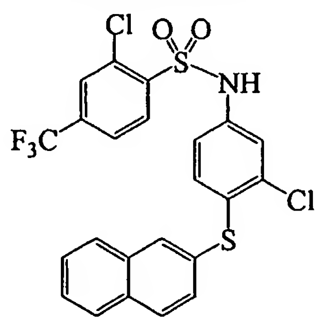


6-Chloro-pyridine-3-sulfonic acid [3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (94).

To a 0.35M solution of 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90)(150 mg, 0.53 mmol) in THF was added pyridine (Aldrich, 0.21 mL, 2.63 mmol) followed by 6-chloro-pyridine-3-sulfonyl chloride (Qorpark, 122 mg, 0.58 mmol). The resulting mixture was stirred for 15 hours. A 1M aqueous solution of HCl (20 mL) was added and the crude reaction mixture was extracted 3x with EtOAc (50 mL). The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was chromatographed (5-15% EtOAc in hexane) to yield 140 mg (58%) of 94 as a pale yellow solid.

^{1}H NMR (DMSO-d_6) δ 10.93 (s, 1H), 8.77 (d, J = 2.0 Hz, 1H), 8.19 (dd, J = 8.4, 2.6 Hz, 1H), 7.97-7.90 (m, 2H), 7.90-7.84 (m, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.59-7.52 (m, 2H), 7.36 (dd, J = 8.6, 1.9 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 7.12-7.04 (m, 2H). MS (M-H)

EXAMPLE 95

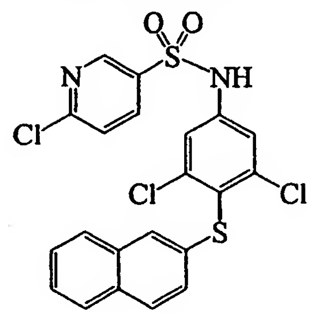


2-Chloro-N-[3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (95)

The title compound was prepared using the method of example 94, starting with 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (150 mg, 0.53 mmol), pyridine (Aldrich, 0.21 mL, 2.63 mmol) and 2-chloro-4-trifluoromethylbenzenesulfonyl chloride (Maybridge, 162 mg, 0.58 mmol) in THF. 250 mg (90%) of title compound (95) was obtained as a pale yellow solid.

^{1}H NMR (DMSO-d_6) δ 11.30 (s, 1H), 8.23 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 7.97-7.84 (m, 3H), 7.84-7.80 (m, 2H), 7.58-7.50 (m, 2H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 7.28 (d, J = 2.3 Hz, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.04 (dd, J = 8.6, 2.3 Hz, 1H). MS (M-H) 526

EXAMPLE 96

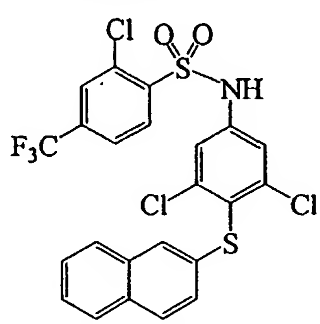


6-Chloro-pyridine-3-sulfonic acid [3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (96)

The title compound was prepared using the method of example 94, starting with 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90) (150 mg, 0.47 mmol), pyridine (Aldrich, 0.19 mL, 2.34 mmol) and 6-chloro-pyridine-3-sulfonyl chloride (Qorpark, 109 mg, 0.52 mmol) in THF. 130 mg (56%) of **96** was obtained as a pale yellow solid.

^{1}H NMR (DMSO-d_6) δ 11.40 (br s, 1H), 8.88 (d, J = 1.9 Hz, 1H), 8.28 (dd, J = 8.4,1.6 Hz, 1H), 7.88-7.80 (m, 3H), 7.76 (d, J = 9.1, 1.8 Hz, 1H), 7.52-7.42 (m, 3H), 7.38 (s, 2H), 7.14 (dd, J = 8.7, 2.0 Hz, 1H). MS (M-H) 493

EXAMPLE 97

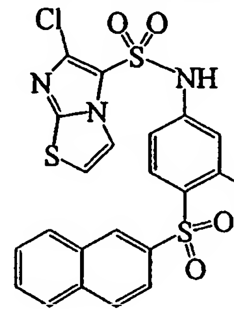


2-Chloro-N-[3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (97)

The title compound was prepared using the method of example 94, starting with 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90)(150 mg, 0.47 mmol), pyridine (Aldrich, 0.19 mL, 2.34 mmol) and 2-chloro-4-trifluoromethylbenzenesulfonyl chloride (Maybridge, 144 mg, 0.52 mmol) in THF. 137 mg (52%) of **97** was obtained as a pale yellow solid.

^{1}H NMR (DMSO-d_6) δ 8.38 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 1.4 Hz, 1H), 8.01 (dd, J = 8.4, 1.1 Hz, 1H), 7.88-7.80 (m, 2H), 7.76-7.71 (m, 1H), 7.51-7.42 (m, 2H), 7.34 (s, 2H), 7.12 (dd, J = 8.6, 2.0 Hz, 1H). MS (M-H) 560

EXAMPLE 98

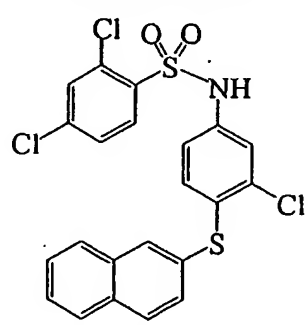


6-Chloro-imidazo[2,1-*b*]thiazole-5-sulfonic acid [3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (98)

The title compound was prepared using the method of example 94, starting with 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (92) (150 mg, 0.53 mmol), pyridine (Aldrich, 0.21 mL, 2.63 mmol) and 6-chloro-imidazo[2,1-*b*]thiazole-5-sulfonyl chloride (Maybridge, 149 mg, 0.58 mmol) in THF. 172 mg (65%) of 98 was obtained as a pale yellow solid.

^{1}H NMR (DMSO-d_6) δ 11.26 (s, 1H), 7.98 (d, J = 4.4 Hz, 1H), 7.96-7.88 (m, 2H), 7.88-7.84 (m, 2H), 7.68 (d, J = 2.4 Hz, 1H), 7.58-7.52 (m, 2H), 7.33-7.28 (m, 2H), 7.14 (d, J = 8.5 Hz, 1H), 7.01 (dd, J = 8.5, 2.4 Hz, 1H), 7.04 (dd, J = 8.6, 2.3 Hz, 1H). MS (M-H) 504

EXAMPLE 99

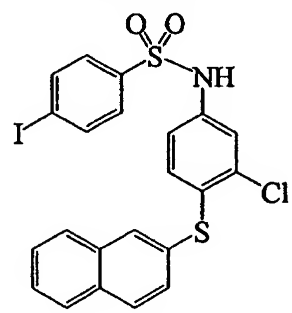


2,4-Dichloro-N-[3-chloro-4-(napthalen-2-ylsulfanyl)-phenyl]-benzene sulfonamide(99)

2,4-Dichloro-N-[3-chloro-4-(napthalen-2-ylsulfanyl)-phenyl]-benzene sulfonamide was synthesized (67%) from 3-chloro-4-(napthalen-2-ylsulfanyl)-phenylamine (92) and 2,4-dichlorobenzenesulfonyl chloride, obtained from Maybridge, in a similar manner as described in example 93.

^{1}H NMR (DMSO-d_6) δ 11.1 (s, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.95-7.88(m, 3H), 7.86-7.81 (m, 2H), 7.65 (dd, J = 8.4 Hz, 1H), 7.57-7.51 (m, 2H), 7.31 (dd, J = 8.6, 1.9 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 8.6, 2.3 Hz, 1H). MS (M-H) 492

EXAMPLE 100

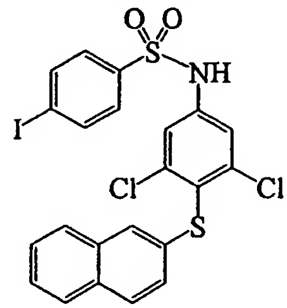


N-[3-Chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-iodo-benzenesulfonamide (100)

The title compound was prepared using the method of example 94, starting with 3-chloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (92)(150 mg, 0.53 mmol), pyridine (Aldrich, 0.21 mL, 2.63 mmol) and 4-iodobenzenesulfonyl chloride (Acros, 175 mg, 0.58 mmol) in THF. 153 mg (53%) of **100** was obtained as a pale yellow solid.

^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 8.01-7.95 (m, 2H), 7.95-7.89 (m, 2H), 7.87-7.82 (m, 2H), 7.59-7.50 (m, 4H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.04 (dd, J = 8.5, 2.2 Hz, 1H). MS (M-H) 550

EXAMPLE 101

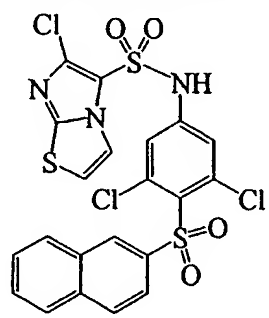


N-[3,5-Dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-iodo-benzenesulfonamide(101)

The title compound was prepared using the method of example 94, starting with 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90) (150 mg, 0.47 mmol), pyridine (Aldrich, 0.19 mL, 2.34 mmol) and 4-iodobenzenesulfonyl chloride (Acros, 155 mg, 0.52 mmol) in THF. 254 mg (93%) of **101** was obtained as a pale yellow solid.

^{1}H NMR (DMSO-d$_6$) δ 11.22 (s, 1H), 8.08-8.02 (m, 2H), 7.88-7.82 (m, 2H), 7.74 (d, J = 7.7 Hz, 1H), 7.65-7.58 (m, 2H), 7.52-7.40 (m, 3H), 7.35 (s, 2H), 7.12 (dd, J = 8.7, 1.9 Hz, 1H). MS (M-H) 584

EXAMPLE 102

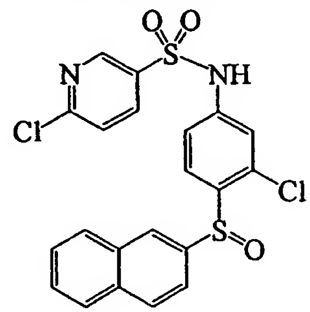


6-Chloro-imidazo[2,1-*b*]thiazole-5-sulfonic acid [3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (102)

The title compound was prepared using the method of example 94, starting with 3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenylamine (90)(150 mg, 0.47 mmol), pyridine (Aldrich, 0.19 mL, 2.34 mmol) and 6-chloro-imidazo[2,1-*b*]thiazole-5-sulfonyl chloride (Maybridge, 132 mg, 0.52 mmol) in THF. 172 mg (65%) of **102** was obtained as a pale yellow solid.

^{1}H NMR (DMSO-d$_6$) δ 11.71 (br s, 1H), 8.02 (d, J = 4.4 Hz, 1H), 7.89-7.82 (m, 2H), 7.77 (m, 1H), 7.72 (d, J = 4.4 Hz, 1H), 7.52-7.432 (m, 3H), 7.35 (s, 2H), 7.11 (dd, J = 8.7, 2.0 Hz, 1H). MS (M-H) 504

EXAMPLE 103

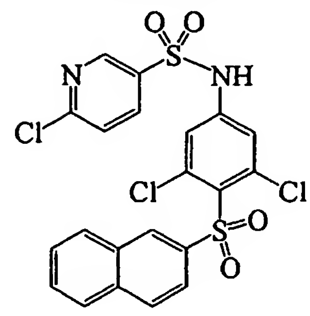


6-Chloro-pyridine-3-sulfonic acid [3-chloro-4-(naphthalene-2-sulfinyl)-phenyl]-amide (103)

To a solution of 6-Chloro-pyridine-3-sulfonic acid [3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (**94**, 55 mg, 0.12 mmol) in CH_2Cl_2 (2 mL), was added dropwise a solution of *m*-chloroperoxybenzoic acid (mCPBA, Aldrich, 36mg, 0.12 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at ambient temperature for 1 hour and diluted with EtOAc (60 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (50 mL), twice with brine solution (50 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was chromatographed (10-25% EtOAc in hexane) to yield 17 mg (30%) of **103** as an off white solid.

^{1}H NMR (DMSO-d$_6$) δ 11.25 (s, 1H), 8.82 (d, J = 2.6 Hz, 1H), 8.43 (d, J = 1.5 Hz, 1H), 8.19 (dd, J = 8.4, 2.6 Hz, 1H), 8.10 (m, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.98 (m, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1 H), 7.70-7.60 (m, 2H), 7.53 (dd, J = 8.7, 1.8 Hz, 1H), 7.40 (dd, J = 8.5, 2.2 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H). MS (M-H) 475

EXAMPLE 104

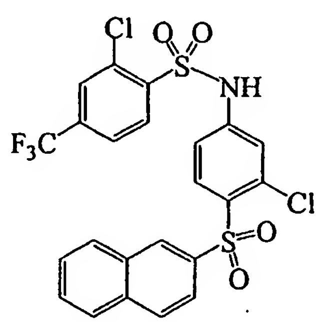


6-Chloro-pyridine-3-sulfonic acid [3,5-dichloro-4-(naphthalene-2-sulfonyl)-phenyl]-amide (104)

To a solution of 6-Chloro-pyridine-3-sulfonic acid [3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (**96**, 20 mg, 0.04 mmol) in CH_2Cl_2 (1 mL), was added dropwise a solution of mCPBA (Aldrich, 36 mg, 0.12 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at ambient temperature overnight and diluted with EtOAc (60 mL). The organic layer was washed twice with 5% aqueous Na2S2O3 solution (20 mL), twice with 1% aqueous $NaHCO_3$ solution (20 mL), and brine solution (20 mL), dried over Na_2SO_4. Removal of the solvent under vacuum gave 21 mg (99%) of **104** as an off white solid.

^{1}H NMR (DMSO-d_6) δ 8.68 (d, J = 2.5 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 8.12-8.05 (m, 2H), 8.02 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 8.7, 2.0 Hz, 1H), 7.76-7.64 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H), 6.93 (s, 2H). MS (M-H) 525

EXAMPLE 105



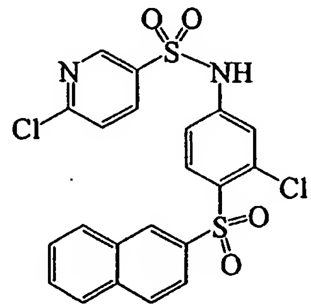
2-Chloro-N-[3-chloro-4-(naphthalene-2-sulfonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide(105)

The title compound was prepared using the method of example 104, starting with 2-Chloro-N-[3-chloro-4-(naphthalen-2ylsulfanyl)-phenyl]-4-

trifluoromethylbenzene-sulfonamide (95, 35 mg, 0.066 mmol), *m*CPBA (Aldrich, 100 mg, 0.33 mmol) in CH_2Cl_2. 38 mg (100%) of 105 was obtained as an off white solid.

^{1}H NMR (DMSO-d_6) δ 11.90 (br s, 1H), 8.62 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.1 Hz 1H), 8.16-8.00 (m, 4H), 7.90 (d, J = 8.5 Hz, 1H), 7.77-7.64 (m, 3H), 7.20 (d, J = 9.0 Hz, 1H), 7.09 (s, 1H). MS (M-H) 558

EXAMPLE 106

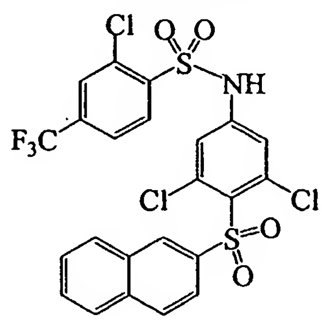


6-Chloro-pyridine-3-sulfonic acid [3-chloro-4-(naphthalene-2-sulfonyl)-phenyl]-amide (106)

The title compound was prepared using the method of example 104, starting with 6-Chloro-pyridine-3-sulfonic acid [3-chloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-amide (94, 15 mg, 0.03 mmol), *m*CPBA (Aldrich, 50 mg, 0.15 mmol) in CH_2Cl_2. 16 mg (100%) of 106 was obtained as an off white solid.

^{1}H NMR (DMSO-d_6) δ 11.60 (br s, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.62 (d, J = 1.8 Hz, 1H), 8.24-8.16 (m, 2H), 8.14 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.76-7.64 (m, 4H), 7.27 (dd, J = 8.8, 2.0 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H). MS (M-H) 491

EXAMPLE 107



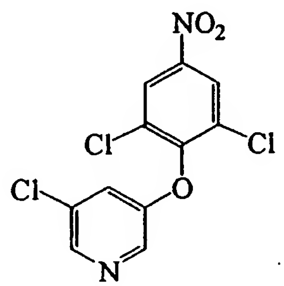
2-Chloro-N-[3,5-dichloro-4-(naphthalene-2-sulfonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (107)

The title compound was prepared using the method of example 104, starting with 2-Chloro-N-[3,5-dichloro-4-(naphthalen-2-ylsulfanyl)-phenyl]-4-trifluoromethylbenzene-sulfonamide (97, 30 mg, 0.05 mmol), *m*CPBA (Aldrich, 80 mg, 0.26 mmol) in CH_2Cl_2. 32 mg (100%) of 107 was obtained as an off white solid.

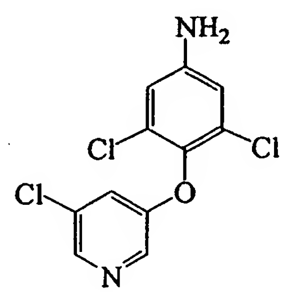
^{1}H NMR (DMSO-d_6) δ 8.59 (d, J = 1.1 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.90 (s, 1H), 7.84-7.77 (m, 2H), 7.75-7.64 (m, 2H), 6.92 (s, 2H). MS (M-H) 592

EXAMPLE 108

This example illustrates the preparation of **108.1** through **108.6**.



108.1



108.2

A solution of potassium *t*-butoxide (1 M in THF; 26.5 mL) was added to a solution of 3,4,5-trichloronitrobenzene (3 g) and 5-chloro-3-hydroxypyridine (1.7 g) in THF (15 mL). The deep red solution was heated at 50°C overnight, then poured into water. The precipitate was collected by filtration and purified by chromatography on silica (10% ethyl acetate/hexanes as eluant) to provide **108.1**.

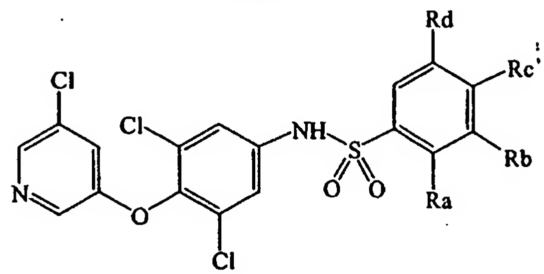
^{1}H NMR (400 MHz) (DMSO-d_6) δ 8.58 (s, 2H); 8.47 (d, J=2 Hz, 1H); 8.41 (d, J=2.6 Hz, 1H); 7.72 (dd, J=2.6, 2 Hz, 1H).

Using the method of Example 2, **108.1** (2.2 g) was converted to the aniline **108.2**.

^{1}H NMR (400 MHz) (DMSO-d_6) δ 8.35 (d, J=2 Hz, 1H); 8.21 (d, J=2.5 Hz, 1H); 7.37 (dd, J=2.5, 2 Hz, 1H); 6.73 (s, 2H); 5.78 (br s, 2H).

The compounds provided in Table 17 were prepared using **108.2** and commercially available substituted benzenesulfonyl chlorides and/or using the intermediates and methods described in the examples above.

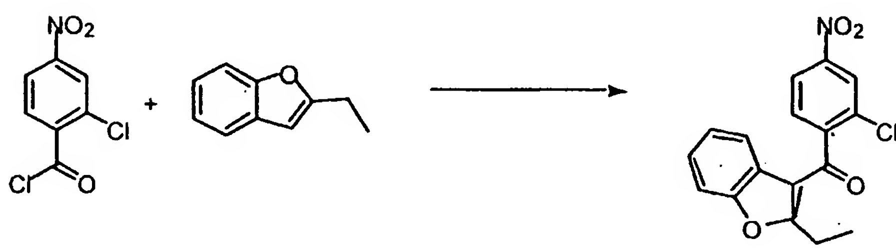
Table 17



	Ra	Rb	Rc	Rd	mp (°C)
108.3	H	Cl	Cl	H	199-200
108.4	Cl	H	Cl	H	166-169
108.5	H	H	I	H	211-214
108.6	Cl	H	CF_3	H	185-189

EXAMPLE 109

This example illustrates the synthesis of **109.1**.



109.1

A round-bottomed flask was charged with 2-chloro-4-nitrobenzoyl chloride (3.50 g, 15.9 mmol), 2-ethylbenzofuran (2.11 g, 14.4 mmol), and anhydrous methylene chloride (20 mL). This was cooled in an ice/water bath and titanium tetrachloride (5.49 g, 28.9 mmol) was added in a dropwise fashion with vigorous stirring. After addition was complete, the reaction was stirred at 0°C for 20 minutes and then was warmed to room temperature for an additional four hours. The reaction was then diluted with 80 mL of methylene chloride and washed twice with 50 mL volumes of 2N HCl and then once with 50 mL of brine. The organics were dried over Na_2SO_4 and concentrated to

a yellow oil. This oil was further purified using silica gel flash chromatography (eluting with 20% hexanes in methylene chloride). The desired fractions were concentrated to give 2.9 g (61%) of ketone **109.1** as an off-white solid. MS ESI m/e: 330.0 (M + H).

EXAMPLE 110

(2,6-Dichloro-4-nitro-phenyl)-acetic acid (110)

To a solution of diethyl malonate (Aldrich, 13.8 mL, 90 mmol) in DMF (60 mL) was added cesium carbonate (Aldrich, 48.9 g, 150 mmol). The mixture was heated to 70 °C and then was added 1,2,3-trichloro-5-nitrobenzene (Aldrich, 13.56 g, 60 mmol). The mixture was stirred at 70°C for 3 hours and cooled to room temperature. A 2M aqueous solution of HCl (50 mL) was added and the crude reaction mixture was extracted 3x with EtOAc (150 mL). The organic layers were combined and washed twice with a brine solution (150 mL), dried over Na_2SO_4, and concentrated under vacuum. The light yellow oil was used for the next reaction without further purification.

The light yellow oil was suspended in 90 mL of 6 N aqueous HCl. The mixture was refluxed overnight (15 hours). The mixture was cooled in the ice bath for 2 hours and filtered. The crude solid product was triturated with CH_2Cl_2/Hexanes to give compound 110 (11.5 g , 77%) as pale brown solid.

^{1}H NMR (DMSO-d_6) δ 13.00 (br s, 1H), 8.23 (s, 2H), 4.16 (s, 2H).

EXAMPLE 111

(2-Chloro-4-nitro-phenyl)-acetic acid (111)

The title compound was prepared using the method of example 110, starting with diethyl malonate (Aldrich, 30.5 mL, 200 mmol), 3,4-dichloronitrobenzene (Aldrich, 19.2 g, 100 mmol), cesium carbonate (Aldrich, 81.5 g, 250 mmol) and 150 mL of aqueous 6N HCl solution. 18.8 g (87%) of compound 111 was obtained as pale yellow solid.

^{1}H NMR (DMSO-d_6) δ 12.80 (br s, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.18 (dd, J = 8.4, 2.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 3.90 (s, 2H).

EXAMPLE 112

2-Amino-4-chloro-benzenethiol hydrochloride (112)

By the procedure of R.L.Danley and D. A. Zazaris (Can. J. Chem. 43, 2610-2612 (1965) sodium tetrasulfide was obtained by dissolving sulfur (Aldrich, 9.6 g,

300 mmol) in molten sodium sulfide nonahydrate (Aldrich, 24.0 g, 100 mmol). This hot liquid was added to a solution of 2,5-dichloronitrobenzene (Aldrich, 38.4 g, 200 mmol) in 95% ethanol (140 mL). After the exothermic reaction had ceased, the mixture was refluxed for 2 hours and filtered while hot. The precipitate was washed with water (50 mL) and ethanol (50 mL) to give 37.7 g of intermediate trisulfide as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 8.83 (d, J = 2.3 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.55 (dd, J = 8.6, 2.3 Hz, 1H).

Concentrated hydrochloric acid (125 mL) was slowly (overnight, 15 hours) added to a well-stirred suspension of the trisulfide (37.7 g) described above and tin (Aldrich, 88 g, 737 mmol) in 95% ethanol (200 mL). After filtration of the hot solution, the filtrate was allowed to stand at room temperature overnight to precipitate the crude product. The precipitate was collected by filtration, washed with1:1 ethanol/concentrated HCl. Recrystalization from 1:1 MeOH/concentrated HCl gave compound 112 (13.8 g) as white needles.

^{1}H NMR (DMSO-d_6) δ 6.96 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H), 6.50 (dd, J = 8.3, 2.3 Hz, 1H).

EXAMPLE 113

2-Amino-4-methyl-benzenethiol hydrochloride (113)

bis-(4-Methyl-2-nitrophenyl)-trisulfide was prepared using the method in example 112, starting from 4-chloro-3-nitro-toluene (Aldrich, 34.3 g, 200 mmol), sulfur (Aldrich, 9.6 g, 300 mmol) and sodium sulfide nonahydrate (Aldrich, 24.0 g, 100 mmol) in 95% EtOH (150 mL). 27.7 g of the trisulfide was obtained as a yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.21 (d, J = 8.3 Hz, 1H), 8.07 (br s, 1H), 7.58 (dd, J = 8.3, 1.3 Hz, 1H), 2.48 (s, 3H).

Reduction of the *bis*-(4-Methyl-2-nitrophenyl)trisulfide as in example 112 gave compound 113 (11.3 g) as a mixture after recrystalization, but which was used directly in subsequent reactions.

EXAMPLE 114

5-Chloro-2-(2,6-dichloro-4-nitro-benzyl)-benzothiazole (114)

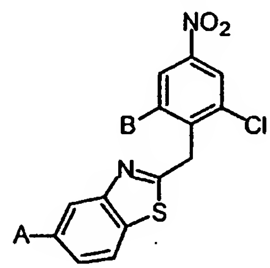
By a modification of the procedure of D.L. Boger (J. Org. Chem. 43, 2296-2297 (1978) a solution of P_2O_5/$MeSO_3H$ (Aldrich, 7.5 g, 1:10, w:w) was treated with 2-amino-4-chloro-benzenethiol hydrochloride (example 112, 1.96 g, 10.0 mmol) and

(2,6-dichloro-4-nitro-phenyl)-acetic acid (example 110, 2.50 g, 10.0 mmol). The resulting mixture was stirred at room temperature for 1 hour, then heated at 90°C overnight (15 hours). After cooled to room temperature, the reaction mixture was poured to ice and the resulting mixture was extracted 3x with EtOAc (50 mL). The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was chromatographed (CH_2Cl_2) to yield 3.7 g (99%) of compound 114 as a pale yellow solid.

^{1}H NMR ($CDCl_3$) δ 8.28 (s, 2H), 7.98 (d, J = 1.9 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.38 (dd, J = 8.5, 1.9 Hz, 1H), 4.87 (s, 2H). MS (M+H) 373

The compounds of Table 18 were prepared using the method of example 114.

Table 18



Example	A	B	yield
114	Cl	Cl	99%
115	Cl	H	98%
116	CF_3	Cl	96%
117	CF_3	H	89%
118	H	Cl	92%
119	H	H	77%
120	Me	Cl	20%
121	Me	H	28%

EXAMPLE 115

5-Chloro-2-(2-chloro-4-nitro-benzyl)-benzothiazole

^{1}H NMR (400MHz, DMSO-d_6) δ 8.35 (d, J = 2.3 Hz, 1H), 8.25 (dd, J = 8.5, 2.4 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.48 (dd, J = 8.6, 2.0 Hz, 1H), 4.77 (s, 2H). MS (M+H) 339

EXAMPLE 116

2-(2,6-Dichloro-4-nitro-benzyl)-5-trifluoromethyl-benzothiazole

^{1}H NMR (DMSO-d_6) δ 8.42 (s, 2H), 8.34 (d, J = 8.4 Hz, 1H), 8.28 (br s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 4.94 (s, 2H). MS (M+H) 407

EXAMPLE 117

2-(2-Chloro-4-nitro-benzyl)-5-trifluoromethyl-benzothiazole

^{1}H NMR ($CDCl_3$) δ 8.33 (d, J = 2.3 Hz, 1H), 8.27 (br s, 1H), 8.14 (dd, J = 8.5, 2.3 Hz, 1H), 7.96 (br d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H) 4.70 (s, 2H). MS (M+H) 371

EXAMPLE 118

2-(2,6-Dichloro-4-nitro-benzyl)-benzothiazole

^{1}H NMR (DMSO-d_6) δ 8.41 (s, 2H), 8.06 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.50-7.38 (m, 2H), 4.94 (s, 2H). MS (M-H) 337

EXAMPLE 119

2-(2-Chloro-4-nitro-benzyl)-benzothiazole

^{1}H NMR ($CDCl_3$) δ 8.35 (d, J = 2.2 Hz, 1H), 8.25 (dd, J = 8.4, 2.2 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 4.76 (s, 2H). MS (M+H) 305

EXAMPLE 120

2-(2,6-Dichloro-4-nitro-benzyl)-5-methyl-benzothiazole

^{1}H NMR (DMSO-d_6) δ 8.41 (s, 2H), 7.91 (d, J = 8.2 Hz, 1H), 7.71 (br s, 1H), 7.25 (d, J = 8.2 Hz, 1H), 4.85 (s, 2H), 2.41 (s, 3H). MS (M+H) 353 .

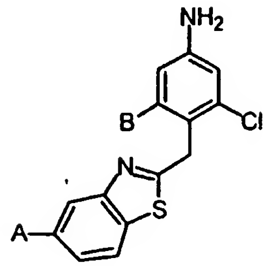
EXAMPLE 121

2-(2-Chloro-4-nitro-benzyl)-5-methyl-benzothiazole

^{1}H NMR (DMSO-d_6) δ 8.35 (d, J = 2.3 Hz, 1H), 8.24 (dd, J = 8.5, 2.3 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.74 (br s, 1H), 7.25 (dd, J = 8.2, 1.0 Hz, 1H), 4.73 (s, 2H), 2.42 (s, 3H). MS (M-H) 317

Reduction of the compounds of Table 18 gave the anilines of Table 19.

Table 19



Example	A	B	Method	yield
122	Cl	Cl	A	100%
123	Cl	H	B	88%
124	CF_3	Cl	A	90%
125	CF_3	H	B	89%
126	H	Cl	B	97%
127	H	H	B	90%
128	Me	Cl	B	97%
129	Me	H	B	97%

Method A: see example 90 Method B: see example 181

EXAMPLE 122

3,5-Dichloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenylamine

^{1}H NMR (DMSO-d_6) δ 8.03 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.45 (dd, J = 8.5, 2.2 Hz, 1H), 6.70 (s, 2H), 5.79 (s, 2H), 4.52 (s, 2H). MS (M+H) 343

EXAMPLE 123

3-Chloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenylamine

^{1}H NMR (DMSO-d_6) δ 8.05-7.95 (m, 2H), 7.43 (dd, J = 8.5, 2.1 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 6.53 (dd, J = 8.2, 2.2 Hz, 1H), 5.44 (s, 2H), 4.36 (s, 2H). MS (M+H) 309.

EXAMPLE 124

3,5-Dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenylamine

^{1}H NMR (DMSO-d_6) δ 8.29 (br s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4Hz, 1H), 6.70 (s, 2H), 5.81(s, 2H), 4.56 (s, 2H). MS (M+H) 377

EXAMPLE 125

3-Chloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenylamine

^{1}H NMR (DMSO-d_6) δ 8.25 (br s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 8.4, 1.3 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 8.2, 2.2 Hz, 1H), 5.46 (s, 2H), 4.40 (s, 2H). MS (M+H) 343

EXAMPLE 126

4-Benzothiazol-2-ylmethyl-3,5-dichloro-phenylamine

^{1}H NMR (DMSO-d_6) δ 7.99 (dd, J = 8.0, 0.6 Hz,, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.45 (td, J = 8.2, 1.2 Hz, 1H), 7.38 (td, J = 8.0, 1.0 Hz, 1H), 6.70 (s, 2H), 5.78(s, 2H), 4.51 (s, 2H). MS (M+H) 309.

EXAMPLE 127

4-Benzothiazol-2-ylmethyl-3-chloro-phenylamine

^{1}H NMR (DMSO-d_6) δ 7.98 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.47 (td, J = 7.9, 1.2 Hz, 1H), 7.38 (td, J = 7.9, 1.0 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 8.2, 2.2 Hz, 1H), 5.44 (s, 2H), 4.35 (s, 2H). MS (M+H) 275

EXAMPLE 128

3,5-Dichloro-4-(5-methyl-benzothiazol-2-ylmethyl)-phenylamine

^{1}H NMR (DMSO-d_6) δ 7.84 (d, J = 8.2 Hz, 1H), 7.73 (br s, 1H), 7.21 (dd, J = 8.2, 1.0 Hz, 1H), 6.69 (s, 2H), 5.77 (s, 2H), 4.48 (s, 2H), 2.43 (s, 3H). MS (M+H) 323.

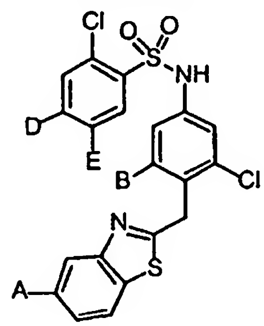
EXAMPLE 129

3-Chloro-4-(5-methyl-benzothiazol-2-ylmethyl)-phenylamine

^{1}H NMR (DMSO-d_6) δ 7.84 (d, J = 8.2 Hz, 1H), 7.73 (s, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 2.1 Hz, 1H), 6.52 (dd, J = 8.2, 2.1 Hz, 1H), 5.41 (s, 2H), 4.32 (s, 2H), 2.43 (s, 3H). MS (M+H) 289.

The compounds of **Table 20** were prepared using the method of example 94 from compounds in **Table 19** and corresponding arylsulfonyl chloride.

Table 20



Example	A	B	D	E	yield
130	Cl	Cl	CF_3	H	83%
131	Cl	Cl	Cl	H	63%
132	Cl	Cl	Cl	Me	73%
133	Cl	H	CF_3	H	78%
134	CF_3	Cl	CF_3	H	74%
135	CF_3	Cl	Cl	H	82%
136	CF_3	H	CF_3	H	55%
137	CF_3	H	Cl	H	26%
138	H	Cl	CF_3	H	67%
139	H	Cl	Cl	H	55%
140	H	Cl	Cl	Me	85%
141	H	H	CF_3	H	64%
142	Me	Cl	CF_3	H	84%
143	Me	H	CF_3	H	88%

EXAMPLE 130

2-Chloro-*N*-[3,5-dichloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.56 (br s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.20 (d, J = 1.1 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 8.00-7.95 (m, 2H), 7.45 (dd, J = 8.6, 2.1 Hz, 1H), 7.23 (s, 2H), 4.62 (s, 2H). MS (M-H) 583

EXAMPLE 131

2,4-Dichloro-*N*-[3,5-dichloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenyl]-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.40 (br s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.70 (dd, J = 8.6, 2.1 Hz, 1H), 7.46 (dd, J = 8.6, 2.0 Hz, 1H), 7.20 (s, 2H), 4.62 (s, 2H). MS (M-H) 549

EXAMPLE 132

2,4-Dichloro-*N*-[3,5-dichloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenyl]-5-methyl-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.33 (br s, 1H), 8.28 (s, 1H), 8.17 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 7.87 (s, 1H), 7.45 (dd, J = 8.6, 1.9 Hz, 1H), 7.22 (s, 2H), 4.61 (s, 2H), 2.40 (s, 3H). MS (M-H) 563

EXAMPLE 133

2-Chloro-*N*-[3-chloro-4-(5-chloro-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.24 (br s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.16 (br s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 8.4, 2.0 Hz, 1H), 4.47 (s, 2H). MS (M-H)z 549

EXAMPLE 134

2-Chloro-*N*-[3,5-dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.56 (s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.26 (br s, 1H), 8.20 (br s, 1H), 7.99 (dd, J = 8.3, 1.0 Hz, 1H), 7.73 (dd, J = 8.2, 1.2 Hz, 1H), 7.24 (s, 2H), 4.67 (s, 2H). MS (M-H) 617

EXAMPLE 135

2,4-Dichloro-*N*-[3,5-dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenyl]-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.41 (s, 1H), 8.29 (br s, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.4, 1.4 Hz, 1H), 7.70 (dd, J = 8.6, 2.0 Hz, 1H), 7.21 (s, 2H), 4.67 (s, 2H). MS (M-H)

EXAMPLE 136

2-Chloro-*N*-[3-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.25 (br s, 1H), 8.32-8.22 (m, 3H), 8.16 (br s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.21 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 4.52 (s, 2H). MS (M-H) 583

EXAMPLE 137

2,4-Dichloro-*N*-[3-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-phenyl]-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.10 (br s, 1H), 8.28 (br s, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.4, 1.4 Hz, 1H), 7.65 (dd, J = 8.6, 2.1 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.10 (dd, J = 8.3, 2.2 Hz, 1H), 4.52 (s, 2H). MS (M-H) 549

EXAMPLE 138

***N*-(4-Benzothiazol-2-ylmethyl-3,5-dichloro-phenyl)-2-chloro-4-trifluoromethyl-benzenesulfonamide**

^{1}H NMR (DMSO-d_6) δ 11.54 (s, 1H), 8.35 (d, J = 8.3 Hz, 1H), 8.20 (br s, 1H), 7.99 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 7.8 Hz, 1H), 7.46 (td, J = 8.0, 1.0 Hz, 1H), 7.40 (td, J = 7.8, 0.9 Hz, 1H), 7.23 (s, 2H), 4.61 (s, 2H). MS (M-H) 549

EXAMPLE 139

***N*-(4-Benzothiazol-2-ylmethyl-3,5-dichloro-phenyl)-2,4-dichloro-benzenesulfonamide**

^{1}H NMR (DMSO-d_6) δ 11.38 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.70 (dd, J = 8.6, 2.0 Hz, 1H), 7.46 (m, 1H), 7.40 (m, 1H), 7.20 (s, 2H), 4.60 (s, 2H). MS (M-H) 515

EXAMPLE 140

N-(4-Benzothiazol-2-ylmethyl-3,5-dichloro-phenyl)-2,4-dichloro-5-methyl-benzenesulfonamide

^{1}H NMR (DMSO-d$_6$) δ 11.32 (s, 1H), 8.17 (s, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.88 (s, 1H), 7.46 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.16 (s, 2H), 4.60 (s, 2H), 2.40 (s, 3H). MS (M-H) 531

EXAMPLE 141

N-(4-Benzothiazol-2-ylmethyl-3-chloro-phenyl)-2-chloro-4-trifluoromethyl-benzenesulfonamide

^{1}H NMR (DMSO-d$_6$) δ 11.23 (br s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.15 (br s, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.46 (td, J = 7.9, 1.0 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 7.11 (dd, J = 8.3, 2.1 Hz, 1H), 4.46 (s, 2H). MS (M-H) 517

EXAMPLE 142

2-Chloro-N-[3,5-dichloro-4-(5-methyl-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

^{1}H NMR (DMSO-d$_6$) δ 11.54 (s, 1H), 8.36 (d, J = 8.2 Hz, 1H), 8.19 (br s, 1H), 8.00 (dd, J = 8.2, 1.0 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.70 (br s, 1H), 7.26-7.18 (m, 3H), 4.58 (s, 2H), 2.40 (s, 3H). MS (M-H) 563

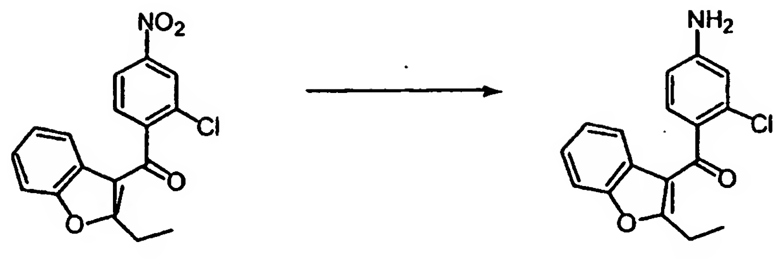
EXAMPLE 143

2-Chloro-N-[3-chloro-4-(5-methyl-benzothiazol-2-ylmethyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide

^{1}H NMR (DMSO-d$_6$) δ 11.22 (br s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.15 (br s, 1H), 7.45 (dd, J = 8.3, 1.1 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.71 (br s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.24-7.19 (m, 2H), 7.05 (dd, J = 8.5, 2.2 Hz, 1H), 4.43 (s, 2H), 2.41 (s, 3H). MS (M-H) 529

EXAMPLE 144

This example illustrates the synthesis of **144.1**.



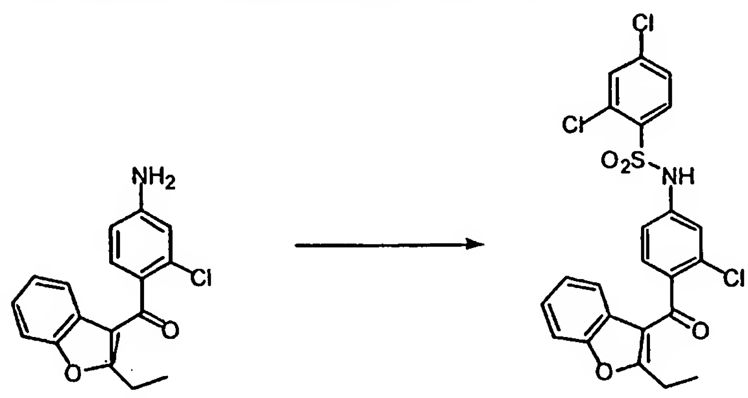
109.1 144.1

Nitro compound **109.1** (1.91 g, 5.8 mmol) was reduced to the corresponding aniline using $SnCl_2 \cdot 2H_2O$ (6.54 g, 29.0 mmol) in EtOAc (40 mL) according to the procedure previously described in Example 30. This yielded 692 mg (40%) of compound **144.1** as a white powder.

MS ESI m/e: 300.0 (M + H).

EXAMPLE 145

This example illustrates the synthesis of **145.1**.



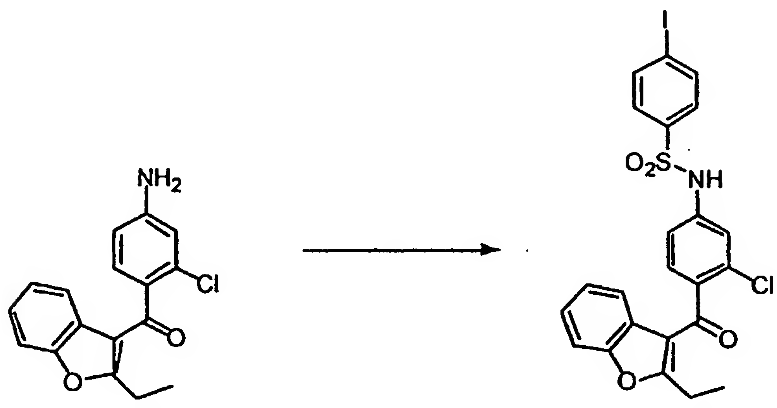
144.1 145.1

A round-bottomed flask was charged with aniline **144.1** (110 mg, 0.37 mmol), 2,4-dichlorobenzenesulfonyl chloride (108 mg, 0.44 mmol), 2,6-lutidine (47 mg, 0.44 mmol), catalytic DMAP, and methylene chloride (2.0 mL). The reaction was allowed to stir overnight. The reaction was then diluted with 20 mL of methylene chloride and washed with 10 mL of 1N HCl and 10 mL of brine. The organics were dried over Na_2SO_4 and concentrated to a yellow oil. This oil was further purified using silica gel flash chromatography. The desired fractions were combined and concentrated to yield 60 mg (32%) of compound **145.1** as a white foam.

[1]H NMR (400MHz) (d_6-DMSO) δ 11.36 (1H, s); 8.12 (1H, d, J=8.6 Hz); 7.94 (1H, d, J=2.1 Hz); 7.68 (1H, dd, J=8.6, 2.1 Hz); 8.63 (1H, d, J=8.4 Hz); 7.47 (1H, d, J=8.4 Hz); 7.36-7.32 (1H, m); 7.27-7.19 (4H, m); 2.54 (2H, q, J= 7.6 Hz); 1.08 (3H, t, J=7.6 Hz). MS ESI m/e: 506.0 (M - H).

EXAMPLE 146

This example illustrates the synthesis of **146.1**.



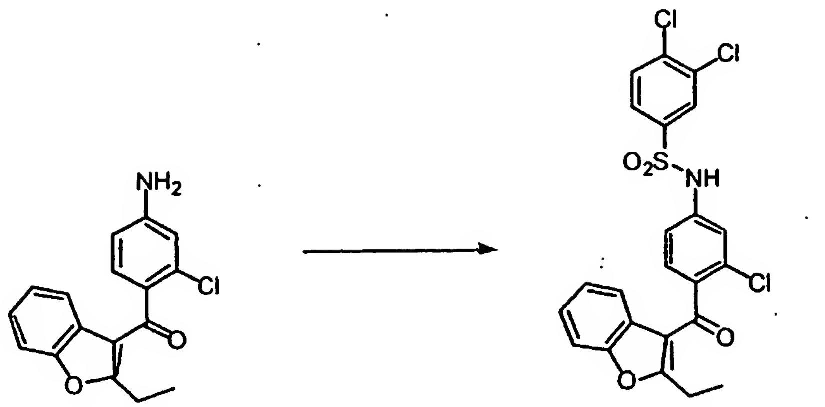
144.1 **146.1**

Aniline **144.1** (111 mg, 0.37 mmol), pipsyl chloride (135 mg, 0.45 mmol), 2,6-lutidine (48 mg, 0.45 mmol), and catalytic DMAP were combined in methylene chloride (2.0 mL) according to the procedure described in Example 77. This yielded 140 mg (67%) of compound **146.1** as a white foam.

[1]H NMR (400MHz) (d_6-DMSO) δ 10.97 (1H, s); 8.01 (2H, d, J=8.4 Hz); 7.63 (1H, d, J=8.4 Hz); 7.58 (2H, d, J=8.4 Hz); 7.46 (1H, d, J=8.4 Hz); 7.34 (1H, m); 7.46-7.20 (4H, m); 2.54 (2H, q, J=7.5 Hz); 1.09 (3H, t, J=7.5 Hz). MS ESI m/e: 563.9 (M - H).

EXAMPLE 147

This example illustrates the synthesis of **147.1**.



144.1 147.1

Aniline **144.1** (108 mg, 0.36 mmol), 3,4-dichlorobenzenesulfonyl chloride (106 mg, 0.43 mmol), 2,6-lutidine (46 mg, 0.43 mmol), and catalytic DMAP were combined in methylene chloride (2.0 mL) according to the procedure described in Example 77. This yielded 113 mg (62%) of compound **147.1** as a white foam.

^{1}H NMR (400MHz) ($CDCl_3$) δ 7.96 (1H, d, *J*=2.2 Hz); 7.66 (1H, dd, *J*=8.4, 2.2 Hz); 7.57 (1H, d, *J*=8.4 Hz); 7.46 (1H, d, *J*=8.3 Hz); 7.34 (1H, d, *J*=8.3 Hz); 7.31-7.26 (3H, m); 7.20-7.15 (2H, m); 2.79 (2H, q, *J*=7.6 Hz); 1.27 (3H, t, *J*=7.6 Hz). MS ESI m/e: 506.0 (M - H).

EXAMPLE 148

This illustrates the synthesis of (2-fluoro-4-nitro-phenyl)acetic acid **148**.

A round-bottomed flask was charged with diethyl malonate (8.6 g, 54 mmol), cesium carbonate (29.3 g, 90 mmol), and anhydrous DMF (36 mL). The mixture was warmed to 70 °C and 2,4-difluoronitrobenzene (5.75 g, 36 mmol) was added in a dropwise fashion with vigorous stirring. The reaction medium immediately turned dark purple. After the addition was complete, the reaction was stirred at 70°C for 30 minutes. After cooling to room temperature, the reaction was quenched with 4 mL of acetic acid and then poured into 300 mL of 0.3 N $HCl_{(aq)}$. The purple color discharged completely upon addition to the acid. The mixture was then neutralized by adding solid $NaHCO_3$ until no gas evolution took place. The mixture was extracted 2 x 150 mL 1:1 diethyl ether:hexanes. The combined organic layers were washed 2 x 100 mL DI water and 1 x 50 mL sat. brine. The organic layer was dried over $MgSO_4$ and concentrated to a yellow oil. This oil was suspended in 40 mL of 6N $HCl_{(aq)}$ and the mixture heated to reflux for

16 h. Upon cooling, crystals separated and were collected by filtration. The crystals were dried under vacuum to yield 2-fluoro-4-nitro-phenylacetic acid (148) as off-white crystals (5.42 g).

^{1}H NMR (400MHz) (d_4-MeOH) δ 8.06 (1H, d); 8.04 (1H, d); 7.60 (1H, t); 3.81 (2H, s).

EXAMPLE 149

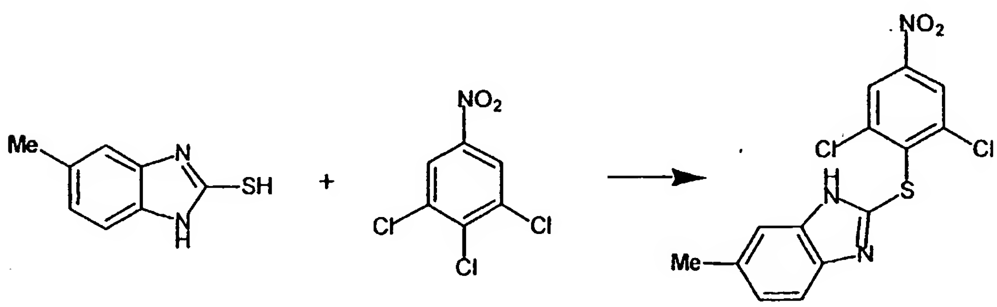
This illustrates the synthesis of 7-chloro-2-(2-fluoro-4-nitro-benzyl)-benzoxazole **149**.

The benzoxazole **149** was formed according to the method of Terashima and Ishi (*Synthesis* 1982, 484-85.). Phenylacetic acid 148 (387 mg, 1.95 mmol), 2-amino-6-chloro-phenol (233 mg, 1.67 mmol, described in *J. Med. Chem.* 1996, *39*, 3435-3450), and boric acid (120 mg, 1.95 mmol) were combined in xylenes (24 mL) and the mixture heated to reflux in a flask equipped with a Dean-Stark trap. After 8 h, the reaction mixture was filtered, concentrated, and the residue purified by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate). Fractions containing benzoxazole 149 were concentrated to a yellow solid (419 mg).

^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1H); 8.00 (dd, 1H); 7.61 (d, 1H); 7.57 (d, 1H); 7.33 (d, 1H); 7.27 (d, 1H) 4.38 (s, 2H). MS (M+H) 307.0

EXAMPLE 150

This illustrates the synthesis of compound **150**.



150

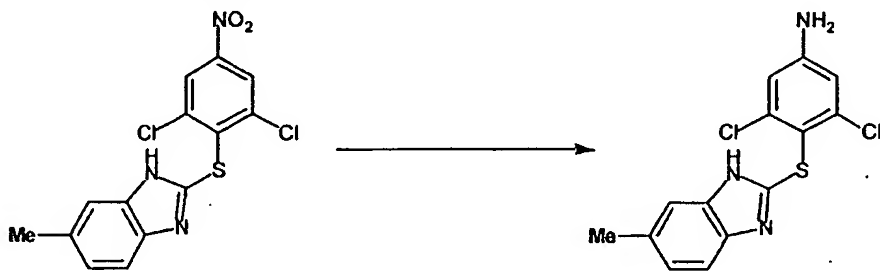
A round-bottomed flask was charged with 2-mercapto-5-methylbenzimidazole (4.84 g, 29.5 mmol), potassium hydroxide (1.66 g, 29.5 mmol), and water (18 mL). This suspension was heated to 120°C for 3.0 hours. Then 3,4,5-trichloronitrobenzene (6.68 g, 29.5 mmol) dissolved in 53 mL of *n*-butanol was added

dropwise while the reaction stirred at 120°C. All the white solids went into solution and the solution proceeded to turn a deep red color. The reaction was left stirring for five days, at which point a yellow precipitate was seen. The reaction was then cooled to room temperature and the precipitate was filtered and washed with distilled water to yield 8.10 g (78%) of compound **150** as canary yellow crystals which were a 50/50 mixture of both possible tautomers.

^{1}H NMR (400MHz) (d_6-DMSO) δ 12.64 (1H, s); 8.48 (2H, d, J=2.2 Hz); 7.34 and 7.27 (1H, 2 tautomeric doublets, J=8.3 Hz); 7.26 and 7.19 (1H, 2 tautomeric singlets); 6.99 and 6.95 (1H, 2 tautomeric doublets, J=8.1 Hz); 2.38 and 2.35 (3H, 2 tautomeric singlets).

EXAMPLE 151

This illustrates the synthesis of compound **151**.



150 **151**

A round-bottomed flask was charged with 8.1 g (22.8 mmol) of compound **150**, 20.6 g (91.4 mmol) of tin dichloride dihydrate, and 150 mL of EtOAc. This was heated to 75°C for 3.0 hours. The reaction was cooled to room temperature, diluted with 300 mL of EtOAc and washed with 250 mL of 2N aqueous KOH solution followed by 200 mL of brine. The organics were dried over sodium sulfate and concentrated to 7.4 g (94%) of **151** as a pale yellow solid that was used without further purification. MS (M+H) 324

EXAMPLE 152

This illustrates the synthesis of compound **152**.

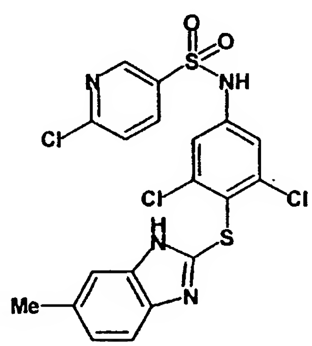
A round-bottomed flask was charged with compound **151** (749 mg, 2.31 mmol), 4-acetylbenzenesulfonyl chloride (1.01 g, 4.62 mmol), 2,6-lutidine (496 mg, 4.62 mmol), acetone (4.0 mL), and a catalytic amount of DMAP. This was stirred at room temperature for 12 hours, after which 2,6-lutidine hydrochloride was seen as a white

precipitate. The reaction was diluted with 40 mL of EtOAc and washed with 30 mL of 1N aqueous HCl followed by 30 mL of brine. The organics were dried over magnesium sulfate and concentrated to a clear oil that was dissolved in 30 mL of THF. To this was added 30 mL of 0.5N aqueous KOH. This was stirred at room temperature for 12 hours, and the reaction color progressed from a light yellow to a deep orange. Next, the pH was brought to 7.0 with 1.0N HCl and the THF was removed *in vacuo*. The remaining aqueous phase was extracted with 100 mL of Et_2O. The organic layer was dried over sodium sulfate and concentrated to a yellow oil that was further purified with silica gel flash chromatography (3:2 hexanes:EtOAc). The desired fractions were combined and concentrated to an oil which was recrystallized from hot EtOAc/hexanes to yield 312 mg (27%) of **152** as an off-white solid. MS (M-H) 504.

^{1}H NMR (d_6-DMSO) δ 12.36 (1H, broad s); 11.39 (1H, broad s); 8.18 (2H, t); 8.03 (2H, t); 7.32 (2H, s); 7.32-7.04 (2H, m); 6.96 (1H, m); 2.62 (3H, s); 2.35 (3H, s).

EXAMPLE 153

This illustrates the synthesis of compound **153**.

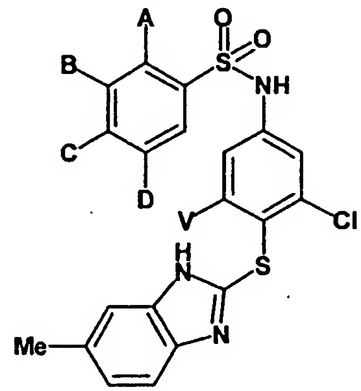


Compound **153** was prepared according to Example 152. In this case, 353 mg (1.1 mmol) of compound **151** was used to give 76 mg (14%) of **153** as white crystals.

^{1}H NMR (d_6-DMSO) δ 12.31 (1H, broad s); 11.42 (1H, broad s); 8.90 (1H, d); 8.29 (1H, dd); 7.81 (1H, d); 7.34 (2H, s); 7.26 (1H, broad s); 7.17 (1H, broad s); 6.92 (1H, d); 2.35 (3H, s). MS (M-H) 497.0.

The additional examples of **Table 21** were prepared according to the method of Example 152.

Table 21



	V	A	B	C	D	m/e (M-H)
152	Cl	H	H	-C(=O)Me	H	504
153	Cl	[2-chloro-5-pyridyl]				497
154	Cl	Me	H	Cl	Me	524
155	Cl	Cl	H	Cl	H	530
156	Cl	Cl	H	CF_3	H	564
157	Cl	Cl	H	Cl	Me	544
158	H	Cl	H	Cl	H	496
159	H	H	Cl	Cl	H	496
160	H	Cl	H	CF_3	H	530
161	H	Cl	H	Cl	Me	510
162	H	H	H	I	H	554
163	H	[2-chloro-5-pyridyl]				463
164	H	Me	H	Cl	Me	490

EXAMPLE 154

^{1}H NMR (d_6-DMSO) δ 12.29 (1H, broad s); 11.37 (1H, broad s); 8.01 (1H, s); 7.57 (1H, s); 7.19-7.33 (4H, m); 6.91 (1H, s); 2.57 (3H, s); 2.38 (3H, s); 1.24 (3H, s). MS (M-H) 524.

EXAMPLE 155

MS (M-H) 529.8. ^{1}H NMR (d_6-DMSO) δ 12.31 (1H, broad s); 11.64 (1H, broad s); 8.18 (1H, d); 7.94 (1H, d); 7.71 (1H, dd); 7.34-7.09 (4H, m); 6.93 (1H, d); 2.33 (3H, s).

EXAMPLE 156

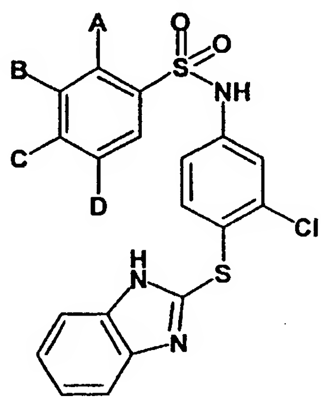
MS (M-H) 564. ^{1}H NMR (d_6-DMSO) δ 12.28 (1H, broad s); 11.80 (1H, broad s); 8.38 (1H, d); 8.19 (1H, s); 8.00 (1H, d); 7.29 (2H, s); 7.24 (1H, broad s); 7.15 (1H, broad s); 6.91 (1H, d); 2.34 (3H, s).

EXAMPLE 157

MS (M-H) 544. ^{1}H NMR (d_6-DMSO) δ 12.29 (1H, broad s); 11.58 (1H, s); 8.22 (1H, s); 7.89 (1H, s); 7.29 (2H, s); 7.24 (1H, broad s); 7.16 (1H, broad s); 6.91 (1H, d); 2.41 (3H, s); 2.34 (3H, s).

The examples of **Table 22** were prepared by analogy to the methods of Examples 150-152.

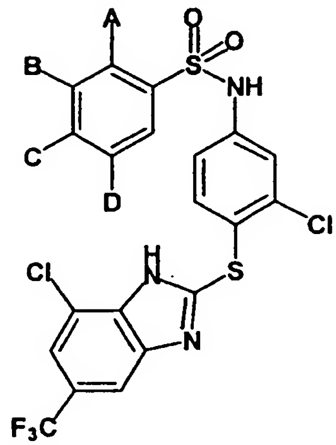
Table 22



	A	B	C	D	m/e (M-H)
165	Cl	H	Cl	Me	496
166	Cl	H	Cl	H	482
167	H	H	I	H	540
168	H	Cl	Cl	H	482
169	Cl	H	CF_3	H	516
170	Me	H	Cl	Me	476

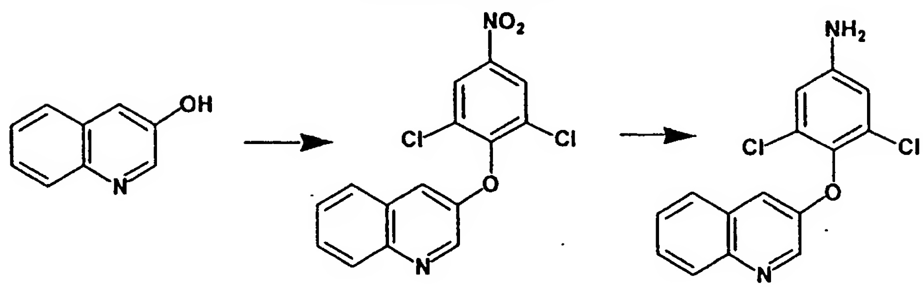
The examples of **Table 23** were prepared by analogy to the methods of Examples 150-152.

Table 23



	A	B	C	D	m/e (M-H)
171	Cl	H	Cl	H	584
172	Cl	H	CF_3	H	618
173	Me	H	Cl	Me	578

EXAMPLE 174



174 175

3-Hydroxyquinoline (prepared according to the procedure of Naumann, *et. al.*, *Synthesis*, 1990, 4, 279-281)) (3 g) and 1,2,3- trichloro-5-nitrobenzene (4.7 g) were dissolved in DMF (80 mL) and heated with cesium carbonate (7.4g) for 2 hr at 60°C. The reaction was poured into ice/water (500 ml). The resulting off-white precipitate was collected by filtration and rinsed with hexane to afford compound **174** as a solid (6.9g) suitable for use in the next reaction.

^{1}H NMR in $CDCl_3$ 8.863 (d, J=2.2Hz, 1H), 8.360 (s, 2H), 8.106 (d, J=8.6Hz, 1H), 7.646 (m, 2H), 7.529 (d, J=8.6Hz, 1H), 7.160 (d, J=2.2Hz, 1H)

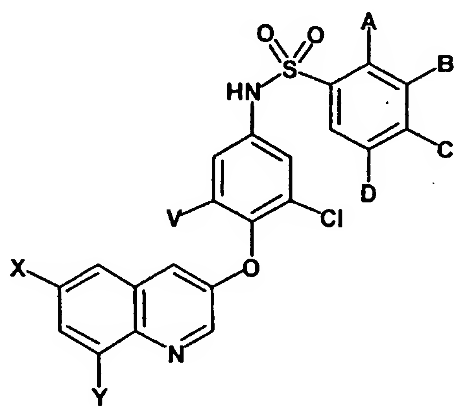
EXAMPLE 175

To a solution of compound **180** (6.9 g) in ethanol/THF/water (ratio 40:20:10) was added ammonium chloride (3.3 g) and powdered iron (3.4g). This mixture was heated to reflux for 5 hr. The hot mixture was then filtered through Celite and concentrated. The residue was dissolved in ethyl acetate and washed with saturated $NaHCO_3$ solution followed by water and then brine. The solution was dried over magnesium sulfate and concentrated to afford compound **175** as an off-white solid (5.6 g).

^1H NMR in (DMSO) δ 8.846 (d, J=2.9Hz, 1H), 8.010 (m, 1H), 7.915 (m, 1H), 7.645 (m, 1H), 7.560 (m, 1H), 7.401 (d, J=2.9Hz, 1H), 6.778 (s, 2H), 5.762 (s, 2H).

Treatment of the aniline **175** with various sulfonyl chlorides according to conventional methods gave the sulfonamides of **Table 24**.

Table 24



Example	X	Y	V	A	B	C	D
176	H	H	Cl	CF_3	H	Cl	H
177	H	H	Cl	Cl	H	CF_3	H
178	H	H	Cl	Cl	H	Cl	H
180	H	H	H	Cl	H	Cl	H
181	$-CO_2Me$	H	Cl	Cl	H	Cl	H
182	H	$-CO_2Me$	Cl	Cl	H	Cl	H
183	$-CO_2H$	H	Cl	Cl	H	Cl	H
184	H	$-CO_2H$	Cl	Cl	H	Cl	H
185	Me	H	Cl	Cl	H	Cl	Me
186	H	H	F	Cl	H	Cl	Me

EXAMPLE 176

^{1}H NMR (DMSO) δ 11.4-11.6 (1H, broad), 8.87 (1H, d, J = 2.9 Hz), 8.15-8.22 (2H, m), 8.00-8.08 (2H, m), 7.87 (1H, d, J = 8.0 Hz), 7.55-7.68 (2H, m), 7.47 (1H, d, J = 2.9 Hz), 7.35 (2H, s). MS (M-H) 545. mp 98.8 °C.

EXAMPLE 177

^{1}H NMR(DMSO) δ 11.58 (1H, s), 8.86 (1H, d, J = 2.9 Hz), 8.38 (1H, d, J = 8.4 Hz), 8.23 (1H, s), 8.01 (1H, d, J = 8.4 Hz), 7.86 (1H, d, J = 8.1 Hz), 7.53-7.68 (2H, m), 7.46 (1H, d, J = 2.9 Hz), 7.34 (2H, s). MS (M-H) 545.0

EXAMPLE 178

^{1}H NMR(d_6-acetone) 9.9 (1H, br s), 8.794 (1H, d, J = 2.9 Hz), 8.23 (1H, d, J = 8.4 Hz), 8.035 (1H, br d, J=8.4 Hz), 7.793 (1H, d, J = 1.5 Hz), 7.78 (1H, m), 7.62-7.70 (2H, m), 7.57 (1H, td, J = 6.8,1.2 Hz), 7.476 (2H, s), 7.364 (1H, d, J=2.6 Hz). MS (M-H) 511.0.

EXAMPLE 179

^{1}H NMR(300MHz/$CDCl_3$) δ 2.43(3H, s), 7.10(1H, d, J=3Hz), 7.26(2H, s), 7.48-7.64(4H, m), 7.96(1H, s), 8.09(1H, d, J= 8.7Hz), 8.78(1H, d, J=3Hz). MS(M+H) 527. mp 233-235 °

EXAMPLE 180

^{1}H NMR(300MHz/$CDCl_3$) δ 7.14(1H, dd, J=2.6Hz,J=8.9Hz), 7.26(1H, d, J=8.9Hz), 7.33(1H, d, J=2.6Hz), 7.56-7.58(2H, m), 7.66-7.69(2H,m), 7.87(1H, m), 7.93(1H, d, J=2.0Hz), 8.00(1H, m), 8.09(1H, d, J=8.5Hz), 8.80(1H, d, J=2.9Hz), 11.06(1H, brs), MS(M+H)) 479. mp 12: °C

EXAMPLE 181

3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-6-carboxylic acid methyl ester (181)

A solution of 3-(4-Amino-2, 6-dichloro-phenoxy)-quinoline-6-carboxylic acid methyl ester (312) (0.93mmol) and 2,4-dichlorobenzenesulfonyl chloride (250mg, 1.02mmol) in Pyridine (0.13ml, 1.53mmol)-CH_2Cl_2 (3.7ml) was stirred at room

temperature for 12 hr. Sat $NaHCO_3$ was added to the reaction mixture, which was then extracted twice with AcOEt. Organic layer was washed by brine, dried over anhydrous $MgSO_4$, and concentrated. Crude residue was purified by column chromatography (Hexane/AcOEt=2/1, 80g of silica gel) to afford compound **181** (237mg, 41%, in 3 steps).

^{1}H NMR (300MHz,DMSO-d_6) δ 3.90 (3H, s), 7.31(2H, s), 7.72 (1H, dd, J=1.8, 7.8Hz), 7.79 (1H, d, J=3.0Hz), 7.96 (1H, d, J=1.8Hz), 8.11 (2H, s), 8.18 (1H, d, J=7.8Hz), 8.64 (1H, s), 8.99 (1H, d, J=3.0Hz), 11.42 (1H, br s). MS (M+H) 571

EXAMPLE 182

3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-8-carboxylic acid methyl ester (182)

To a solution of 3-(4-Amino-2, 6-dichloro-phenoxy)-quinoline-8-carboxylic acid methyl ester (**315**) (1.26mmol) in Pyridine (0.15ml, 1.80mmol) and CH_2Cl_2 (5ml), was added 2,4-Dichlorolbenzenesulfonyl chloride (381mg, 1.55mmol). The mixture was stirred at room temperature for 12hr. Sat $NaHCO_3$ was added to the reaction mixture, which was then extracted twice with AcOEt. Organic layer was washed by Brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (Hexane/AcOEt=2/1, 80g of silica gel) to afford compound **182** (506mg, 70%) as a white solid.

^{1}H NMR (300MHz,DMSO-d_6) δ 3.91 (3H, s), 7.31(2H, s), 7.57-7.65 (2H, m), 7.72 (1H, dd, J=2.1, 8.6Hz), 7.83(1H, d, J=8.6Hz), 7.96 (2H, d, J=2.1Hz), 8.03 (1H, d, J=8.6Hz), 8.18 (1H, d, J=8.6Hz), 8.94 (1H, d, J=2.1Hz), 11.4 (1H, br s), MS(M+H) 571

EXAMPLE 183

3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-6-carboxylic acid (183)

To a solution of 3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-6-carboxylic acid methyl ester (**181**) (200mg, 0.35mmol) in THF/MeOH(2ml/2ml) was added 4N NaOH (0.1ml, 0.4mmol). This mixture was refluxed for 2.5 hr. The reaction mixture was cooled to room temperature and was neutralized with 2N HCl, and then concentrated. The residue was extracted twice with AcOEt. Organic layer was washed by Brine, dried over anhydrous $MgSO_4$, and

concentrated to give a solid. Crude product was recrystallized by Hexane/AcOEt to afford compound **183**(153mg, 78%).

^{1}H NMR (300MHz,DMSO-d_6) δ 7.16 (2H, s), 7.62(1H, dd, J=2.0, 8.5Hz), 7.73 (1H, d, J=2.9Hz), 7.82 (1H, s), 8.08-8.11 (3H, m), 8.60 (1H, s), 8.95 (1H, d, J=2.9Hz), 13.2 (1H, br s), MS (M+H) 557. mp 228-2

EXAMPLE 184

3-[2,6-Dichloro-4- (2,4-dichloro-benzenesulfonylamino)-phenoxy]-quinoline-8-carboxylic acid (184)

To a solution of 3-[2,6-Dichloro-4- (2-chloro-4-trifluoromethyl-benzenesulfonylamino)-phenoxy]-quinoline-8-carboxylic acid methyl ester (**183**) (402mg, 0.7mmol) in THF/MeOH=0.1ml/0.3ml was added 4N NaOH (0.2ml, 0.77mmol). The mixture was refluxed for 12hr. After cooling to room temp. the reaction mixture was filtered to remove insoluble materials. The filtrate was concentrated and the residue was dissolved in aq NH_4Cl and extracted twice with AcOEt. Organic layer was washed by Brine, and dried over anhydrous $MgSO_4$, and concentrated to afford compound **184** (197mg, 50%) as a white solid.

^{1}H NMR (300MHz,DMSO-d_6) δ 7.32 (2H, s), 7.70-7.81(2H, m), 7.90 (1H, d, J=2.2Hz), 7.96 (1H, d, J=2.2Hz), 8.17-8.19 (1H, m), 8.22-8.24 (1H, m), 8.38-8.39 (1H, m), 9.11 (1H, d, J=2.2Hz), 11.4 (1H, br s), 15.4 (1H, br s). MS (M+H) 557. mp 263-266 °C.

EXAMPLE 185

2,4-Dichloro-N- [3,5-dichloro-4- (6-methyl-quinoln-3-yloxy)-phenyl]-5-methyl-benzenesulfonamide(185)

To a solution of 3,5-Dichloro-4- (6-methyl-quinlin-3-yloxy)-phenylamine (339) (400mg, 1.25mmol) in Pyridine (0.12ml, 1.48mmol)- CH_2Cl_2 (4ml) was added 2,4-Dichloro-5-methylbenzenesulfonyl chloride (325mg, 1.25mmol). The mixture was stirred at room temperature for 12hr. The reaction mixture was concentrated and the residue was purified by column chromatography (Hexane/AcOEt=2/1, 80g of silica gel) to provide compound (**185**) (453mg, 66%) as a white solid.

^{1}H NMR (300MHz,DMSO-d_6) δ 2.41 (3H, s), 2.44(3H, s), 7.31 (3H, s), 7.49 (1H, d, J=8.7Hz), 7.61 (1H, s), 7.88-7.91 (2H, m), 8.19 (1H, s), 8.74 (1H, d, J=3.0Hz), 11.3 (1H, br s), MS (M+H) 541 mp 228-230°C.

EXAMPLE 186

PART 1

Preparation of 3-chloro-5-fluoro-4-(quinolin-3-yloxy)nitrobenzene (**186.1**)

To a solution of 3,4-Difluoronitrobenzene 1.00g in conc.H_2SO_4 (20ml), was added portionwise Cl_2O in CCl_4(25ml, prepared as described by Cady G. H. et. al in Inorg. Synth. Vol 5, p156(1957)). The mixture was stirred at room temperature overnight. The mixture was poured into crashed ice and extracted with Et_2O (30mlx3). Combined ether layers were washed with 10%Na_2SO_3 and brine, and dried over Na_2SO_4. The solvent was concentrated to Ca. 10ml(This solution contains 3-Chloro-4,5-difluoronitrobenzene). This solution was diluted with acetone (60ml), and then 3-hydroxyquinoline 0.75g and K_2CO_3 2.2g were added to this solution. The mixture was heated to reflux for 1.5 hr. After cooling the reaction mixture was filtered through a short celite pad. The filtrate was concentrated to give an oil, which was then purified by column chromatography (silica gel, AcOEt:Hexane=1:5) to provide the intermediate compound **186.1** (0.980g) as a yellow oil.

PART 2

Preparation of 3-Chloro-5-fluoro-4-(quinolin-3-yloxy)phenylamine (**186.2**)

To a solution of 3-Chloro-5-fluoro-4-(quinolin-3-yloxy)nitrobenzene (**186.1**) (0.980g) and NH_4Cl (1.64g) in EtOH(50ml) – H_2O (5ml), was added iron powder (1.92g). The mixture was heated to reflux for 1hr. After cooling the reaction mixture was filtered through short celite pad. The filtrate was concentrated, diluted with sat. $NaHCO_3$ and extacted with AcOEt(30mlx3). The combined organic layeres were washed with brine and dried over Na_2SO_4. Concentration of solvent afford crude product, which was purified by column chromatography (silicagel, AcOEt:Hexane=1:3) to provide aniline **186.2** (0.420g) as a colorless solid.

PART 3

Preparation of N-[3-chloro-5-fluoro-4-(quinolin-3-yloxy)phenyl]-2,4-dichloro-5-methyl-benzenesulfonamide (**186**)

To a solution of 3-chloro-5-fluoro-4-(quinolin-3-yloxy)phenylamine **(186.2)** (0.420g) in pyridine(2.2ml), was added 2,4-dichloro-5-methylbenzenesulfonylchloride 0.360g. The mixture was stirred at room for 1hr. The reaction mixture was purified directly by column chromatography (silicagel, AcOEt:Hexane=1:3). The product was triturated by hexane to give title compound (0.522g). (73%) as a solid.

NMR(300MHz/$CDCl_3$) δ 2.43(3H, s), 7.05(1H, d, J=2.6Hz), 7.09-7.11(1H, m), 7.21(1H, d, J=2.6Hz), 7.36(1H, brs), 7.49-7.66(4H, m), 7.96(1H, s), 8.10(1H, d, J=8.2Hz), 8.80(1H, brs). MS (M+H) 511. mp 187 °C.

EXAMPLE 187

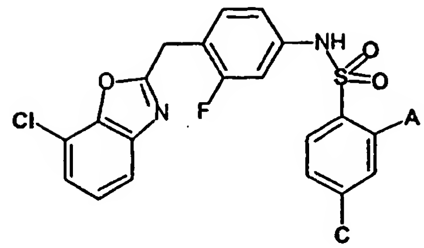
This illustrates the synthesis of 7-chloro-2-(2-fluoro-4-amino-benzyl)-benzoxazole **187**.

To the nitro compound **149** (419 mg, 1.4 mmol) in ethyl acetate (10 mL) was added $SnCl_2 \cdot 2H_2O$ (1.2 g, 5.5 mmol). The reaction mixture was heated to reflux for 30 minutes. After allowing to cool to room temperature, the reaction mixture was poured into 13 mL of saturated 2N $KOH_{(aq)}$. The layers were separated, and the aqueous layer extracted 1 x 30 mL ethyl acetate . The combined organic layers were washed with saturated brine and dried over Na_2SO_4. After concentration, the yellow oil was purified by radial chromatography (2 mm silica gel layer Chromatatron plate, 3:2 hexanes:ethyl acetate). Eluant containing the desired product was concentrated to 194 mg of aniline **187**.

^{1}H NMR (d_6-acetone) δ 7.58 (dd, 1H); 7.39-7.31 (m, 2H); 7.11 (t, 1H); 6.50-6.43 (m, 2H); 4.94 (bs, 2H); 4.21 (s, 2H). MS (M+H) 277.1.

EXAMPLE 188

This illustrates the synthesis of sulfonamide **188**.



Example 188 A= C=Cl

Example 189 A=H; C=COMe

To aniline **187** (95 mg, 0.34 mmol) in acetone (1 mL) was added 2,6-lutidine (60 µL, 0.51 mmol) and 2,4-dichloro-benzenesulfonyl chloride (93 mg, 0.38 mmol, Maybridge Chemical Co.). After 16 hours, the reaction mixture was filtered through a 1 cm plug of silica gel. After concentration, the yellow oil was purified by radial chromatography (1 mm silica gel layer Chromatatron plate, 3:1 hexanes:ethyl acetate). Eluant containing the product was concentrated and the residue recrystallized from hot hexanes/ethyl acetate. Filtration and drying under vacuum yielded the sulphonamide **188** as light yellow crystals (65 mg).

^{1}H NMR (d_6-acetone) δ 9.70 (bs, 1H); 8.16 (d, 1H); 7.71 (d, 1H); 7.60-7.56 (m, 2H); 7.42-7.32 (m, 3H); 7.11-7.09 (m, 2H); 4.32 (s, 2H). MS (M-H) 482.9.

EXAMPLE 189

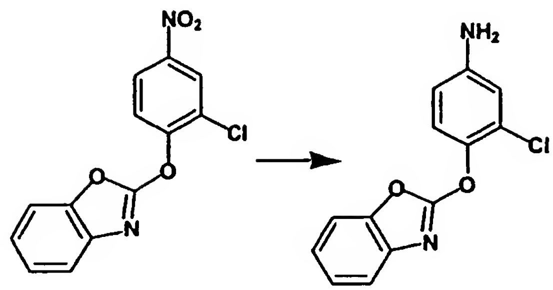
This illustrates the synthesis of sulfonamide **189**.

By the method of example **188**, using the aniline 187 and 4-acetyl-benzenesulfonyl chloride compound **189** was obtained as light yellow crystals.

^{1}H NMR (d_6-acetone) δ 9.50 (bs, 1H); 8.11 (d, 2H); 8.11 (d, 2H); 7.98 (d, 2H); 7.57 (d, 1H); 7.42-7.32 (m, 3H); 7.12-7.06 (m, 2H); 4.33 (s, 2H); 2.61 (s, 3H). MS (M-H): 482.9.

EXAMPLE 190

This illustrates the synthesis of compound **190**.



190 191

2-chloro-4-nitro-phenol (2 g, 11.5 mmol) was dissolved in DMF (5 mL) and treated with Cs_2CO_3 (3.7 g, 11.5 mmol). The reaction mixture was heated to 50 °C until gas evolution stopped. 2-chlorobenzoxazole (2.65 g, 17.3 mmol) was added, and then the reaction mixture was warmed to 75 °C. After 5 hours, the heat was removed and the reaction mixture was poured into 150 mL of deionized water with vigorous stirring. The precipitate was collected by filtration and rinsed several times with distilled water. The product was dried under a stream of air for 15 minutes, then under vacuum overnight to afford compound 190 as an off-white solid (3.4 g), homogeneous by TLC (R_f=0.55, 3:1 hexanes:ethyl acetate). MS (M+H) 291.0

EXAMPLE 191

This illustrates the synthesis of compound **191**. See above.

A round-bottomed flask was charged with 2.01 g (6.93 mmol) of compound **190**, 50 mL of isopropyl alcohol, and 20 mL of THF. Then 0.5 mL of a 50/50 suspension of Raney Nickel in water was added. The reaction was then stirred under a hydrogen balloon at room temperature for 24 hours. Raney Nickel was removed by filtration through celite, and the solution was concentrated *in vacuo*. Recrystallization from ethanol and hexanes gave 1.01 g (60%) of aniline **191** as off-white needles. MS (M+H) 261.0.

EXAMPLE 192

This illustrates the synthesis of compound **192**. (See Table below)

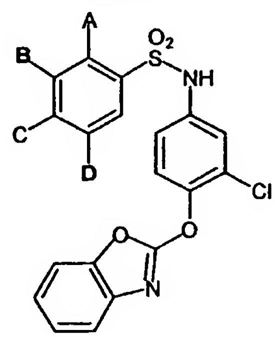
A round-bottomed flask was charged with aniline **191** (144 mg, 0.55 mmol), 2,4-dichlorobenzenesulfonyl chloride (221 mg, 0.55 mmol), 2,6-lutidine (97 mg, 0.55 mmol), catalytic DMAP, and acetone (3.0 mL). The reaction was allowed to stir overnight. The reaction was then diluted with 20 mL of methylene chloride and washed

with 10 mL of 1N HCl and 10 mL of brine. The organics were dried over Na_2SO_4 and concentrated to a clear oil. This oil was further purified using silica gel flash chromatography. The desired fractions were combined and concentrated to a stiff foam. The product was recrystallized from methylene chloride and hexanes to yield 165 mg (65%) of compound **192** as white crystals.

^{1}H NMR (d_6-DMSO) δ 11.21 (1H, s); 8.12 (1H, d, J=8.6 Hz); 7.92 (1H, d, J=2.1 Hz); 7.69-7.63 (3H, m); 7.48 (1H, dd, J=7.3, 4.3 Hz); 7.31-7.29 (3H, m); 7.18 (1H, dd, J=9.0, 2.6 Hz). MS (M-H) 467.0

The additional examples of **Table 25** were prepared from aniline **191** and the corresponding sulfonyl chloride by the method of example 192.

Table 25



Example	A	B	C	D	(M-H)
192	Cl	H	Cl	H	467
193	Cl	H	Cl	Me	481
194	Me	H	Cl	Me	
195	Cl	H	CF_3	H	501
196	H	H	-COMe	H	441
197	[2-chloro-5-pyridyl]				434

EXAMPLE 193

^{1}H NMR (d_6-DMSO) δ 11.14 (1H, s); 8.14 (1H, s); 7.87 (1H, s); 7.65-7.61 (2H, m); 7.50-7.48 (1H, m); 7.32-7.28 (3H, m); 7.19 (1H, dd, J=8.9, 2.7 Hz); 2.40 (3H, s). MS (M-H) 481

EXAMPLE 194

^{1}H NMR (d_6-DMSO) δ 10.92 (1H, s); 7.94 (1H, s); 7.65-7.60 (2H, m); 7.54 (1H, s); 7.49 (1H, dd, J=4.8,1.6 Hz); 7.31-7.27 (3H, m); 7.16 (1H, dd, J=8.9, 2.6 Hz); 2.56 (3H, s); 2.36 (3H, s).

EXAMPLE 195

^{1}H NMR (d_6-DMSO) δ 11.36 (1H, s); 8.32 (1H, d); 8.18 (1H, s); 7.97 (1H, dd); 7.64 (2H, dd); 7.47 (1H, d); 7.31 (3H, m); 7.20 (1H, dd). MS (M-H) 501.

EXAMPLE 196

^{1}H NMR (400MHz) (d_6-DMSO) δ 10.96 (1H, s); 8.15 (2H, dd); 7.97 (2H, d); 7.62 (2H, d); 7.49 (1H, t); 7.31 (3H, m); 7.22 (1H, t); 2.62 (3H, s). MS (M-H) 441.0

EXAMPLE 197

^{1}H NMR (d_6-DMSO) δ 11.04 (1H, s); 8.89 (1H, s); 8.34 (1H, dd); 8.05 (1H, d); 7.87 (1H, d); 7.67 (1H, dd); 7.52 (1H, t); 7.38 (1H, d); 7.25 (1H, t); 7.19 (1H, t); 2.62 (3H, s). MS (M-H) 434.0

EXAMPLE 198

Preparation of 3-Chloro-4-(quinolin-3-yloxy)nitrobenzene(198)

To a solution of 3-hydroxyquinoline (1.00g) and 3-chloro-4-fluoronitrobenzene (1.21g) in Acetone(20ml), was added K_2CO_3 (2.86g). The mixture was refluxed for 1hr. After cooling the reaction mixture was filtered through a short celite pad. The filtrate was concentrated to provide compound 198 (2.07g, quant.) as a brown oil.

^{1}H NMR(300MHz/$CDCl_3$) δ 7.02(1H, d, J=9.1Hz), 7.61(1H, m), 7.72-7.80(3H, m), 8.10-8.18(2H, m), 8.45(1H, d, J=2.7Hz), 8.82(1H, d, J=2.8Hz).

EXAMPLE 199

Preparation of 3-Chloro-4-(quinolin-3-yloxy)phenylamine (199)

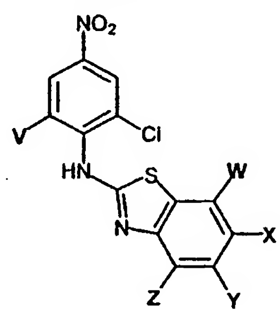
To a solution of nitrobenzene 198 (2.07g) and NH_4Cl (1.84g) in EtOH (40ml) – H_2O (10 ml), was added iron powder (1.92g). The mixture was heated to

reflux for 1hr. After cooling the reaction mixture was filtered through short celite pad. The filtrate was concentrated, diluted with sat. $NaHCO_3$ (30ml) and extacted with AcOEt(30ml). The combined organic layers were washed with brine (30ml) and dried over Na_2SO_4. Concentration of the solvent afforded the aniline **199** (1.77g, 95%)as a yellow solid.

^{1}H NMR(300MHz/$CDCl_3$) δ 3.77(2H, brs), 6.63(1H, dd, J=2.7Hz, J=8.6Hz), 6.83(1H, d, J=2.7Hz), 6.99(1H, d, J=8.6Hz),7.24(1H, d, J=2.8Hz), 7.49(1H, m), 7.56-7.64(2H, m), 8.08(1H, m), 8.86(1H, J=2.8Hz)

The structures for examples **200-208** are illustrated in **Table 26.**

Table 26



EXAMPLE	V	W	X	Y	Z	MS(M-H)
200	Cl	H	Cl	H	H	372
201	H	H	H	H	H	304
203	H	Cl	H	H	Me	352
204	Cl	Cl	H	Cl	H	406
205	Cl	H	H	H	Me	354 (M+H)
206	Cl	H	Me	H	H	354 (M+H)
207	Cl	Cl	H	H	H	372
208	Cl	H	- SO_2Me	H	H	416

EXAMPLE 200

This illustrates the synthesis of compound **200**.

2-amino-6-chlorobenzothiazole (3.68 g, 20 mmol) and 1,2,3-trichloro-5-nitrobenzene (4.53 g, 20 mmol) were dissolved in anhydrous DMSO (10 mL). Solid K_2CO_3 (3.04 g, 22 mmol) was added and the reaction mixture heated to 150 °C for 4

hours. Let cool, then poured into 200 mL deionized water. A fine yellow solid precipitated which was collected by filtration after attempts to dissolve the product in ethyl acetate failed. The yellow solid was suspended in 100 mL of ethyl acetate and heated to reflux. After cooling to room temperature, filtration, rinsing with ethyl acetate followed by hexanes, and drying under vacuum provided the nitro compound **200** as a yellow powder. (1.06 g)

^{1}H NMR (d_6-DMSO) δ 8.37 (s, 2H); 7.76 (bs, 1H); 7.30 (dd, 1H); 7.23 (bs, 1H). MS (M-H) 372

EXAMPLE 201

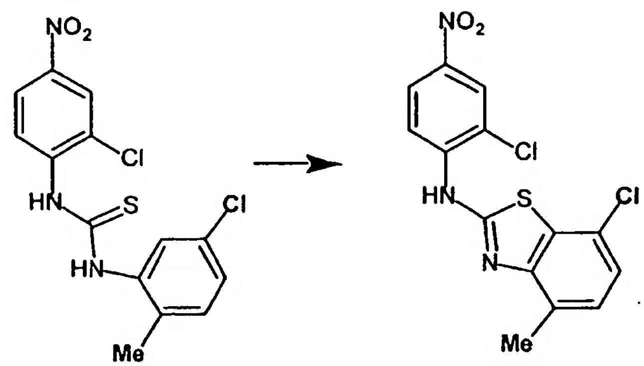
This illustrates the synthesis of compound **201**.

To a solution of 2-chloro-4-nitro aniline (2 g) and potassium t-butoxide (12 mmol) in THF (18 mL) was added a solution of 2-chlorobenzothiazole (2.75 g) in THF (6 mL). The mixture was heated at reflux overnight then quenched into water (100 mL). The product is extracted with methylene chloride and purified by flash chromatography to afford compound **201** (300 mg) as a yellow solid.

^{1}H NMR (d6-acetone) δ 9.74 (br s, 1H), 9.214 (br d, 1H), 8.346 (m, 2H), 7.891 (d, J=8 Hz, 1H), 7.794 (d, J=8 Hz, 1H), 7.466 (t, J=7.2 Hz, 1H), 7.321 (t, J=7.2 Hz, 1H). MS (M-H) 304.

EXAMPLE 202

This illustrates the synthesis of compound **202**.



202 **203**

By the method of Abuzar et al, (Ind. J. Chem 20B, 230-233 (1981)) 2-chloro-4-nitro phenylisothiocyanate (Lancaster) (0.95g) was coupled with 2-amino-4-chlorotoluene (0.69g) in reluxing acetone to form the mixed thiourea **202** (1.5g).

^{1}H NMR (DMSO) δ 10.021 (s, 1H), 9.789 (s, 1H), 8.373 (m, 1H), 8.197 (m, 2H), 7.441 (d, J=1.6Hz, 1H), 7.315 (d, J=8.4 Hz, 1H), 7.268 (dd, J= 8.4, 2. Hz, 1H), 2.237 (s, 3H). MS (M+H) 356. Anal. calcd.: 47.20 %C, 3.11 %H, 11.80 %N; found: 47.24 %C, 3.15 %N, 11.69%N.

EXAMPLE 203

This illustrates the synthesis of compound **203.**

To a cool solution of thiourea **202** (0.63 g) in chloroform (6 mL) was added bromine (0.6 g) slowly. The mixture was then heated to reflux for 2 hours. On cooling, the solids were collected by filtration and then triturated with acetone to afford benzothiazole **203** as its HBR salt (0.5 g).

^{1}H NMR (DMSO) δ 8.989 (br d, J=8.4 Hz, 1H), 8.365 (d, J=2.4 Hz, 1H), 8.291 (dd, J=9.2, 2.8 Hz, 1H), 7.259 (m, 2H), 5.4 (br s), 2.557 (s, 3H). MS (M-H) 352. Anal.: calc for M+0.9HBr: 39.38 %C, 2.34 %H, 9.84 %N; found: 39.44 %C, 2.35 %H, 9.66 %N.

EXAMPLE 204

This illustrates the synthesis of compound **204.**

By the method of examples **202** and **203**, 2,6-dichloro-4-nitrophenylisothiocyanate (GB1131780 (1966)) was coupled with 3,5-dichloroaniline to form the corresponding mixed thiourea which was cyclized with bromine to afford benzothiazole **204** suitable for use in the next reaction. MS (M-H) 406

EXAMPLE 205

By the method of example **200,** benzothiazole **205** was prepared in 78% yield as a yellow solid. MS (M+H) 354.

EXAMPLE 206

By the method of example **200,** benzothiazole **206** was prepared in 30% yield as a yellow solid. MS (M+H) 354

EXAMPLE 207

This illustrates the synthesis of compound **207.**

2,7-dichlorobenzothiazole (Example 73.2) (0.85 g, 4.2 mmol) and 2,6-dichloro-4-nitroaniline (2.1 g, 10.4 mmol) were dissolved in anhydrous DMSO (10 mL). Solid Cs_2CO_3 (4.1 g, 12.5 mmol) was added and the reaction mixture heated to 80 °C for 16 hours. Let cool, then poured into 200 mL DI water. Excess cesium carbonate was neutralized with acetic acid. The aqueous layer was extracted 2 x 100 mL of ethyl acetate. The combined organic layers were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated to a yellow-brown solid. The insolubility of this compound prevented purification, so the crude material was used directly in the next reaction.

^{1}H NMR (400MHz) (d_6-acetone) δ 10.35 (bs, 1H); 8.36 (s, 2H); 7.37 (t, 1H); 7.30 (dd, 1H); 7.21 (dd, 1H). MS (M-H) 371.9.

EXAMPLE 208

By the method of examples **202** and **203**, 2,6-dichloro-4-nitrophenylisothiocyanate (GB1131780 (1966)) was coupled with methyl-(4-aminophenyl)-sulfone to form the corresponding mixed thiourea which was cyclized with bromine to afford benzothiazole **208** suitable for use in the next reaction.

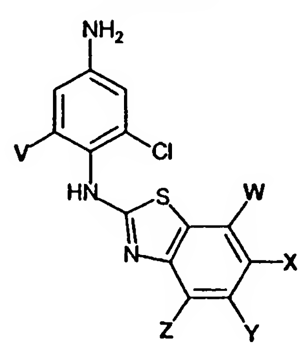
^{1}H NMR (DMSO) δ 8.44 (s, 2H), 8.28 (br s, 2H), 7.82 (br d, 1H), 7.41 (br d, 1H), 3.19 (s, 3H). MS (M-H) 416.

EXAMPLES 209-216

Reduction of the nitro derivatives of **Table 26** by the methods of example 32 or example 175 gave the corresponding anilines illustrated in **Table 27**.

The structures for examples 209-216 are illustrated in **Table 27**.

Table 27



EXAMPLE	V	W	X	Y	Z	MS(M+H)
209	Cl	H	Cl	H	H	344
210	H	H	H	H	H	276
211	H	Cl	H	H	Me	324
212	Cl	Cl	H	Cl	H	378
213	Cl	H	H	H	Me	324
214	Cl	H	Me	H	H	324
215	Cl	Cl	H	H	H	344
216	Cl	H	- SO_2Me	H	H	388

EXAMPLE 209

^{1}H NMR (d_6-acetone) δ 8.78 (s, 1H); 7.29 (d, 1H); 7.41 (d, 1H); 7.27 (d, 1H); 6.86 (s, 2H); 5.42 (s. 1H). MS (M+H) 344

EXAMPLE 212

^{1}H NMR (DMSO) δ 10.09 (s, 1H), 7.48 (br s, 1H), 7.31 (d, J=1.8 Hz, 1H), 6.72 (s, 2H), 5.91 (br s, 2H). MS (M+H) 378

EXAMPLE 215

Crude **207** was reduced with $SnCl_2$•$2H_2O$ according to the procedure of Example **32** to afford compound **215** as a greenish/gray solid after recrystallization from hot ethyl acetate/hexanes (1.14 g).

^{1}H NMR (d_6-acetone) δ 8.87 (bs, 1H); 7.40 (dd, 1H); 7.30 (t, 1H); 7.11 (d, 1H); 6.87 (s, 2H); 5.44 (bs, 2H). MS (M+H) 344.0

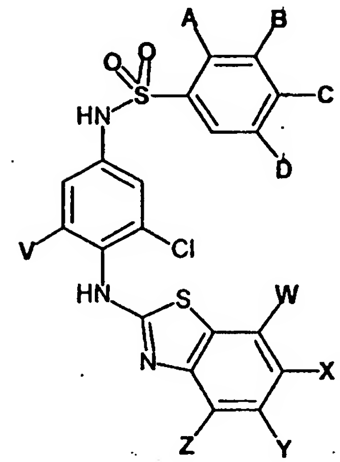
EXAMPLE 216

^{1}H NMR (DMSO) δ 10.08 (s, 1H), 8.31 (s, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.57 (d, J=8.4 Hz, 1H), 6.73 (s, 2H), 5.90 (s, 2H), 3.17 (s, 3H). MS (M-H) 388

EXAMPLES 217-238

Sulfonation of the anilines of **Table 27** by the methods of example 3 or 192 provides the compounds illustrated in **Table 28.**

Table 28



Example #	A	B	C	D	V	W	X	Y	Z	MS(M-H)
217	Cl	H	Cl	Me	Cl	H	Cl	H	H	564
218	Cl	H	Cl	H	Cl	H	Cl	H	H	550
219	Cl	H	CF_3	H	Cl	H	Cl	H	H	584
220	Cl	H	Cl	H	H	H	H	H	H	482
221	Cl	H	CF_3	H	H	H	H	H	H	516
222	Cl	H	Cl	Me	H	H	H	H	H	496
223	Cl	H	Cl	H	Cl	H	Cl	H	Me	530
224	Cl	H	CF_3	H	Cl	H	Cl	H	Me	564
225	Cl	H	Cl	H	Cl	Cl	H	Cl	H	584
226	Cl	H	CF_3	H	Cl	Cl	H	Cl	H	618
227	Cl	H	Cl	Me	Cl	Cl	H	Cl	H	598
228	Cl	H	Cl	H	Cl	H	H	H	Me	530
229	Cl	H	CF_3	H	Cl	H	H	H	Me	564
230	Cl	H	Cl	Me	Cl	H	H	H	Me	544
231	H	H	-COMe	H	Cl	H	H	H	Me	-
232	Cl	H	Cl	H	Cl	H	Me	H	H	530
233	Cl	H	CF_3	H	Cl	H	Me	H	H	564
234	Cl	H	Cl	Me	Cl	H	Me	H	H	544
235	Cl	H	Cl	H	Cl	Cl	H	H	H	550
236	Cl	H	CF_3	H	Cl	Cl	H	H	H	584
237	Cl	H	Cl	H	Cl	H	- SO_2Me	H	H	594

238	Cl	H	CF_3	H	Cl	H	$-SO_2Me$	H	H	628

EXAMPLE 217

^{1}H NMR (d_6-acetone) δ 9.19 (bs, 1H); 8.51 (s, 1H); 7.74 (d, 1H); 7.72 (s, 1H); 7.43 (s, 2H); 7.37 (d, 1H); 7.28 (dd, 1H); 2.46 (s, 3H). MS (M-H) 563.9

EXAMPLE 218

^{1}H NMR (d_6-acetone) δ 9.19 (bs, 1H); 8.22 (d, 1H); 7.78 (d, 1H); 7.74 (d, 1H); 7.67 (dd, 1H); 7.43 (s, 2H); 7.37 (d, 1H); 7.28 (dd, 1H). MS (M-H) 549.8

EXAMPLE 219

^{1}H NMR (d_6-acetone) δ 10.05 (bs, 1H); 9.22 (bs, 1H); 8.45 (d, 1H); 8.06 (s, 1H); 7.98 (d, 1H); 7.73 (m, 1H); 7.45 (s, 2H); 7.36 (d, 1H); 7.28 (dt, 1H). MS (M-H) 583.8.

EXAMPLE 223

^{1}H NMR (DMSO) δ 10.96 (1H, s), 10.11 (1H, s), 8.12-8.22 (1H, broad), 8.06 (1H, d, 8.6), 7.90 (1H, d, J = 2.1 Hz), 7.65 (1H, dd, J = 8.6, 2.1 Hz), 7.23 (1H, d, J = 3.5 Hz), 7.10-7.20 (3H, m), 2.44 (3H, s). MS (M-H) 529.8

EXAMPLE 224

^{1}H NMR (DMSO) δ 11.11 (1H, s), 10.11 (1H, s), 8.27 (1H, d, J = 8.0 Hz), 8.16 (2H, s), 7.94 (1H, d, J = 8.6 Hz), 7.10-7.26 (4H, m), 2.43 (3H, s). MS (M-H) 563.9. mp 192.6 °C

EXAMPLE 225

^{1}H NMR (DMSO) δ 11.49 (s, 1H), 10.44 (s, 1H), 8.164 (d, J=8.4 Hz, 1H) 7.95 (d, J=2 Hz, 1H), 7.71 (dd, J=8.4, 2Hz, 1H), 7.50 (br s, 1H), 7.35 (d, J=1.6 Hz, 1H), 7.25 (s, 2H). MS (M-H) 584

EXAMPLE 226

^{1}H NMR(DMSO) δ 11.59 (s, 1H), 10.40 (s, 1H), 8.368 (d, J=8.4 Hz, 1H), 8.20 (br s, 1H), 8.00 (br d, J=8.4 Hz, 1H), 7.48 (br s, 1H), 7.344 (t, J=1.6 Hz, 1H), 7.274 (d, J=1.6 Hz, 2 H). MS (M-H) 618.

EXAMPLE 227

^{1}H NMR (DMSO) δ 11.37 (s, 1H), 10.40 (s, 1H), 8.19 (br s, 1H), 7.90 (m, 1H), 7.53 (br s, 1H), 7.35 (br s, 1H), 7.25 (br s, 2 H), 2.415 (s, 3H). MS (M-H) 598.

EXAMPLE 228

^{1}H NMR (d_6-DMSO) δ 11.44 (1H, broad s); 9.96 (1H, broad s); 8.33 (1H, d); 8.19 (1H, s); 7.99 (1H, dd); 7.43 (1H, broad s); 7.26 (2H, s); 7.07 (1H, d); 6.97 (1H, t); 2.35 (3H, s). MS (M - H) 529.9.

EXAMPLE 229

^{1}H NMR(d_6-DMSO) δ 11.26 (1H, broad s); 9.96 (1H, broad s); 8.12 (1H, d); 7.93 (1H, d); 7.69 (1H, dd); 7.43 (1H, broad s); 7.23 (2H, s); 7.08 (1H, d); 6.97 (1H, t); 2.36 (3H, s). MS (M-H) 564.

EXAMPLE 230

^{1}H NMR (d_6-DMSO) δ 11.23 (1H, broad s); 9.96 (1H, broad s); 8.14 (1H, s); 7.88 (1H, s); 7.43 (1H, broad s); 7.24 (2H, s); 7.08 (1H, d); 6.97 (1H, t); 2.40 (3H, s); 2.36 (3H, s). MS (M-H) 543.9.

EXAMPLE 231

^{1}H NMR (d_6-DMSO) δ 11.02 (1H, broad s); 9.96 (1H, broad s); 8.16 (2H, d); 7.97 (2H, d); 7.43 (1H, broad s); 7.26 (1H, s); 7.07 (1H, d); 6.97 (1H, t); 2.62 (3H, s); 2.36 (3H, s).

EXAMPLE 232

^{1}H NMR (d_6-DMSO) δ 11.28 (1H, broad s); 9.79 (1H, broad s); 8.13 (1H, d); 7.93 (2H, d); 7.70 (1H, dd); 7.44 (1H, broad s); 7.21 (3H, s); 7.05 (1H, d); 2.30 (3H, s). MS (M-H) 529.9.

EXAMPLE 233

^{1}H NMR (d_6-DMSO) δ 11.43 (1H, broad s); 9.79 (1H, broad s); 8.34 (1H, d); 8.19 (1H, s); 7.99 (1H, d); 7.44 (1H, broad s); 7.24 (3H, s); 7.04 (1H, d); 2.30 (3H, s). MS (M - H) 564.

EXAMPLE 234

^{1}H NMR (d_6-DMSO) δ 11.22 (1H, broad s); 9.79 (1H, broad s); 8.15 (1H, s); 7.89 (1H, s); 7.44 (1H, broad s); 7.23 (3H, s); 7.04 (1H, d); 2.41 (3H, s); 2.31 (3H, s). MS (M - H) 543.9.

EXAMPLE 235

^{1}H NMR (d_6-acetone) δ 9.92 (bs, 1H); 9.35 (bs, 1H); 8.23 (d, 1H); 7.78 (d, 1H); 7.67 (dd, 1H); 7.45 (s, 2H); 7.36-7.29 (m, 2H); 7.16 (dd, 1H). MS (M-H) 549.8.

EXAMPLE 236

^{1}H NMR (d_6-acetone) δ 8.45 (d, 1H); 8.06 (s, 1H); 7.97 (d, 1H); 7.46 (s, 2H); 7.33-7.29 (m, 2H); 7.16 (dd, 1H). MS (M-H) 583.8.

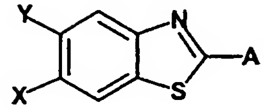
EXAMPLE 237

^{1}H NMR (DMSO) δ 11.43 (br s, 1H), 10.40 (br s, 1H), 8.33 (br s, 1H), 8.16 (d, J= 8 Hz, 1H); 7.94 (d, J=2 Hz, 1H), 7.753 (dd, J=8.2, 2 Hz, 1H), 7.71 (dd, J=8.4, 2 Hz, 1H),7.55 (br s, 1H), 7.265 (s, 2H), 3.22 (s, 3H). MS (M-H) 594.

EXAMPLE 238

^{1}H NMR (DMSO) δ 11.55 (br s, 1H), 10.40 (br s, 1H), 8.38 (m, 2H), 8.22 (br s, 1H), 8.02 (br d, 1H), 7.77 (dd, J= 8.4, 2 Hz, 1H), 7.55 (br s, 1H), 7.295 (s, 2H), 3.19 (s, 3H). MS (M-H) 628.

Table 29



Example #	A	X	Y	yield
239	SH	H	CF_3	92%
240	SH	H	CO_2H	66%
241	SH	CN	H	97%
243	SH	H	CN	49%
245	SH	H	Me	53%
250	Cl	H	Cl	96%

EXAMPLE 239

2-Mercapto-5-trifluoromethyl-benzothiazole (239)

In analogy to the procedure of Chaudhuri, N. *Synth. Commun.* **1996**, *26, 20*, 3783, *O*-ethylxanthic acid, potassium salt (Lancaster, 7.5 g, 46.9 mmol) was added to a solution of 2-bromo-5-trifluoromethylphenylamine (Aldrich, 5.0 g, 20.8 mmol) in *N,N*-dimethylformamide (DMF, 30 mL). The mixture was heated to reflux for 4 hours. After cooling to room temperature, the mixture was poured into ice water and acidified with 2N HCl. The solid product was collected by filtration. Recrystalization from $CHCl_3$/Hexanes gave **239** (4.5 g , 92%) as a white solid.

^1H NMR (400MHz, DMSO-d_6) δ 14.00 (s, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.62 (dd, J = 8.4, 1.0 Hz, 1H), 7.48 (d, J = 1.0 Hz, 1H). MS (M-H) 234.

EXAMPLE 240

2-Mercapto-benzothiazol-5-carboxylic acid (240)

2-Mercapto-benzothiazol-5-carboxylic acid (**240**) (3.5 g, 66%) was synthesized from 4-chloro-3-nitro-benzoic acid, obtained from Fluka, and potassium dithiocarbonate O-ethyl ester, obtained from Lancaster, according to the procedure of Chaudhuri, N. *Synth. Commun.* **1996**, *26, 20*, 3783.

^1H NMR (400MHz, DMSO-d_6) δ 14.0 (s, 1H), 13.3 (bs, 1 H), 7.85-7.79 (m, 3 H).

EXAMPLE 241

2-Mercapto-benzothiazole-6-carbonitrile (241)

The title compound was prepared using the method of example 239, starting with 4-amino-3-chloro-benzonitrile (Lancaster, 5.0 g, 32.7 mmol), *O*-ethylxanthic acid, potassium salt (Lancaster, 11.8 g, 73.7 mmol) in DMF (40 mL). The mercaptobenzothiazole (**241**) (6.1 g, 97%) was obtained as a pale brown solid.

^{1}H NMR (DMSO-d_6) δ 14.10 (s, 1H), 8.22 (d, J = 1.3 Hz, 1H), 7.82 (dd, J = 8.4, 1.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H). MS (M-H) 191.

EXAMPLE 242

3-Amino-4-chloro-benzonitrile (242)

The title compound was prepared using the method of example 32, starting with 4-chloro-3-nitro-benzonitrile (Fluka, 11.0 g, 60 mmol), tin chloride dihydrate (Aldrich, 67.8 g, 300 mmol). 9.0 g (98%) of crude compound **242** was obtained as a yellowish solid.

^{1}H NMR (DMSO-d_6) δ 7.39 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 2.0 Hz, 1H), 6.93 (dd, J = 8.2, 2.0 Hz, 1H), 5.88 (s, 2H). MS (M-H) 151.

EXAMPLE 243

2-Mercapto-benzothiazole-5-carbonitrile (243)

The title compound was prepared using the method of example 239, starting with 3-amino-4-chloro-benzonitrile (**242**) (9.0 g, 59.0 mmol), *O*-ethylxanthic acid, potassium salt (Lancaster, 21.23 g, 132.7 mmol) in DMF (90 mL). 5.6 g (49%) of compound **243** was obtained as a pale brown solid.

^{1}H NMR (DMSO-d_6) δ 14.10 (br s, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.70 (dd, J = 8.3, 1.1 Hz, 1H), 7.60 (br s, 1H). MS (M-H) 191.

EXAMPLE 244

2-Bromo-5-methyl-phenylamine (244)

The title compound was prepared using the method of example 32, starting with 1-bromo-4-methyl-2-nitro-benzene (Lancaster, 10.1 g, 46.7 mmol), tin chloride dihydrate (Aldrich, 52.8 g, 233 mmol). 8.2 g (94%) of crude compound **244** was obtained as a pale brown oil.

^1H NMR (DMSO-d_6) δ 7.18 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 2.1 Hz, 1H), 6.93 (dd, J = 8.1, 1.8 Hz, 1H), 5.34 (s, 2H), 2.26 (s, 3H). MS (M+H)186.

EXAMPLE 245

2-Mercapto -5-Methyl-benzothiazole (245)

The title compound was prepared using the method of example 239, starting with 2-bromo-5-methyl-phenylamine **(244)** (4.48 g, 24.0 mmol), *O*-ethylxanthic acid, potassium salt (Lancaster, 8.70 g, 54 mmol) in DMF (35 mL). The mercaptobenzothiazole **245** was obtained as an pale brown solid (2.31 g, 53%).

^1H NMR (DMSO-d_6) δ 13.70 (br s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.15-7.10 (m, 2H), 2.38 (s, 3H). MS (M-H) 180.

EXAMPLE 246 & 247

2,3-Dichloro-5-nitrobenzoic acid (246)

2,3-Dichlorobenzoic acid, obtained from Aldrich, (40 g, 0.21mole) was added portion wise to a –20 °C concentrated H_2SO_4, obtained from Acros, (233 mL) solution which was fitted with a mechanical overhead stirrer. During the addition process, a separate flask containing concentrated H_2SO_4 (50 mL) was cooled to 0 °C and fuming HNO_3, obtained from Acros, (16.6 mL) was slowly added. This solution was then added dropwise to the 2,3-Dichlorobenzoic acid solution at a rate which kept the reaction mixture at or slightly below –15 °C. After the addition was complete the resulting solution was allowed to warm to 10 °C over 3 hours. The crude solid material was filtered through a fritted filter funnel, washed with cold H_2O (200 mL), and dried under a stream of air followed by high vacuum to yield 21.7 g (44%) of product **(246)** which contained 4% of the undesired regioisomer (2,3-Dichloro-6-nitrobenzoic acid **247**) based on ^1H NMR analysis. The filtrate was slowly poured over ice and additional solid precipitated. This solid was observed to be a 3:1 mixture of 2,3-dichloro-6-nitrobenzoic acid **(247)** to 2,3-dichloro-5-nitrobenzoic acid **(246)** based on ^1H NMR analysis.

2,3-Dichloro-5-nitrobenzoic acid **(246)**: ^1H NMR (DMSO-d_6) δ 8.63 (d, J = 2.7 Hz, 1H), 8.47 (d, J = 2.7 Hz, 1H). 2,3-Dichloro-6-nitrobenzoic acid: **(247)**. ^1H NMR (DMSO-d_6) δ 8.22 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H).

EXAMPLE 248

1-(2,3-Dichloro-5-nitro-phenyl)-ethanone (248)

To thionyl chloride, obtained from Aldrich, (125 mL) at 0 °C was slowly added 2,3-Dichloro-5-nitrobenzoic acid (**246**) (21.7 g, 91.9 mmol). The ice bath was taken away and the resulting solution was heated to reflux for 17 hours (note: acid completely dissolves upon heating). After cooling to ambient temperature, the excess thionyl chloride was removed under vacuum and the resulting acid chloride was allowed to stand under high vacuum for 15 h and used in the next step without further purification. To a 1M solution of NaH, 60% oil dispersion obtained from Aldrich, (11.39 g, 285 mmol) in DMF at 0 °C was slowly added diethylmalonate, obtained form Aldrich, (14.65 mL, 96.5 mmol) dropwise and the resulting solution was allowed to stir for 30 minutes. The acid chloride was dissolved in DMF (184 mL) and slowly added via cannula to the reaction mixture. The resulting solution was then allowed to stir for 16 h as ambient temperature was reached followed by recooling to 0 °C and slowly quenching with excess 2M aqueous HCl (200 mL). To the crude reaction was added H_2O (500 mL) and EtOAc (500 mL). The aqueous layer was extracted three times with EtOAc (500 mL), the organic layers were combined, washed four times with saturated aqueous brine (500 mL), dried over Na_2SO_4, and concentrated under vacuum to yield an oil which was used in the next step without further purification. The resulting product was dissolved in 111 mL of a 7.7/5/1 AcOH/H_2O/conc. H_2SO_4, solution and heated to reflux for 22 hours. The AcOH was removed under vacuum followed by EtOAc addition (200 mL). The solution was neutralized using 2M aqueous NaOH, extracted 3 times with EtOAc (200 mL). The combined organic layers were washed twice with saturated aqueous brine (200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography (30% CH_2Cl_2 in hexane) to yield 17.6 g (82%) of ketone **248** as a light brown solid.

^1H NMR (DMSO-d_6) δ 8.61 (d, J = 2.6 Hz, 1H), 8.48 (d, J = 2.6 Hz, 1H), 2.65 (s, 3H).

EXAMPLE 249

2-Methoxy-4-nitrobenzenethiol (249)

2-Methoxy-4-nitrobenzenethiol (249) was prepared according to the method of Price and Stacy , *J. Amer. Chem. Soc.* 68, 498-500 (1946)) in 67% yield from 1-chloro-2-methoxy-4-nitro-benzene, obtained from Aldrich._.

^{1}H NMR (DMSO-d_6) δ 7.8 (bd, J = 8.4 Hz, 1H), 7.73 (bs, 1H), 7.62 (bd, J = 8.4 Hz, 1H), 5.8 (bs, 1H), 3.95 (s, 3H). MS (M-H) 184.

EXAMPLE 250

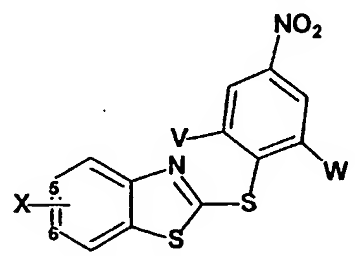
2,5-Dichloro-benzenethiazole(250)

5-Chloro-benzenethiazole-2-thiol, obtained from Aldrich, (2 g, 9.9 mmol) was added slowly to sulfuryl chloride, obtained from Aldrich, (20 mL) and stirred for 1 h followed by heating to 50 °C for 15 minutes. The mixture was cooled, poured slowly over ice water and stirred for 30 minutes. The product precipitated out of solution as a yellow solid and was collected by vacuum filtration and dried under a stream of air followed by high vacuum to give 1.92 g (96%) of compound **250**. .

^{1}H NMR (400MHz, DMSO-d_6) δ 8.18 (d, J = 8.7 Hz, 1H), 8.1 (d, J = 2.0, 1H), 7.59 (dd, J = 8.7, 2.1 Hz, 1H).

Table 30

Table 30 illustrates the structures of examples **251-264**.



#	X	V	W	Yield
251	5-Cl	Cl	-COMe	52%
252	5-CF_3	Cl	H	92%
253	5-CO_2H	Cl	H	66%
254	5-CO_2Me	Cl	H	100%
255	5-CO_2H	Cl	Cl	100%
256	5-CO_2Me	Cl	Cl	100%

257	5-Cl	H	-OMe	75%
258	5-CF_3	Cl	Cl	99%
259	5-CF_3	Cl	-COMe	75%
260	6-CN	Cl	Cl	99%
261	6-CN	Cl	H	93%
262	5-CN	Cl	Cl	99%
263	5-CN	Cl	H	92%
264	5-Me	Cl	-COMe	98%

EXAMPLE 251

1-[3-Chloro-2-(5-chloro-benzothiazol-2-ylsulfanyl)-5-nitro-phenyl]-ethanone (251)

To a 0.55M solution of 5-chloro-2-mercaptobenzothiazole, obtained from Aldrich, (5.55 g, 27.5 mmol) in DMF at ambient temperature was added NaH, 60% oil dispersion obtained from Aldrich, (1.2 g, 30.0 mmol) portionwise followed by 1-(2,3-Dichloro-5-nitro-phenyl)-ethanone (**248**) (5.83 g, 25 mmol). The reaction solution turned from bright orange to deep red upon acetophenone addition and was heated to 60 °C for 1 hour. The mixture was allowed to cool for a couple of minutes and the product was precipitated out of solution by the slow addition of H_2O (250 mL). After 1h of stirring the product was collect by vacuum filtration using a buAnal. calcd.: er funnel, dried under a stream of air for 3h, and triterated with a 1:1 $MeOH/CH_2Cl_2$ solution (200 mL) to yield 5.2 g (52%) of **251** as an orange solid. An additonal 3.77 g (39%) could be isolated by purifying the mother liquor using column chromatography (dry load,100% CH_2Cl_2).

^1H NMR (DMSO-d_6) δ 8.68 (d, J = 2.5 Hz, 1H), 8.6 (d, J = 2.4 Hz, 1H), 8.05 (d, = 8.6 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.6, 2.0 Hz, 1H), 2.65 (s, 3H).

EXAMPLE 252

2-(2-Chloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (252)

2-(2-Chloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (**252**) was prepared (92%) from 2-chloro-1-fluoro-4-nitrobenzene, obtained from Aldrich, and

5-trifluoromethyl-benzothiazol-2-thiol **(239)** in a similar manner as described in example 251.

[1]H NMR (DMSO-d_6) δ 8.58 (d, J = 2.4 Hz, 1H), 8.38-8.32 (m, 2 H), 8.05 (d, = 8.6 Hz, 1H), 8.28 (dd, J = 8.7, 2.5 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.8 (bd, J = 9.9 Hz, 1H).

EXAMPLE 253

2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazol-5-carboxylic acid (253)

2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazol-5-carboxylic acid was prepared (66%) from 2-mercapto-benzothiazol-5-carboxylic acid **(240)** and 2-chloro-1-fluoro-4-nitrobenzene, obtained from Aldrich, in a similar manner as described in example 251.

[1]H NMR (DMSO-d_6) δ 8.56 (d, J = 2.4 Hz, 1H), 8.42 (bs, 1 H), 8.27 (dd, = 8.7, 2.4 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.7 Hz, 1H), 8.0 (dd, J = 8.4, 1.4 Hz, 1H). MS (M-H) 365.

EXAMPLE 254

2-(2-Chloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (254)

To a 0.25M solution of 2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazol-5-carboxylic acid **(253)**, (1.38 g, 3.8 mmol) in 10% MeOH in THF was added a 2M solution of (trimethylsilyl)diazomethane in hexane, obtained from Aldrich, (2.1 mL, 4.18 mmol) and the resulting solution was allowed to stir for 18 hours. The crude reaction mixture was concentrated under vacuum to yield 1.4 g (100%) of ester **254** which was taken on without further purification.

[1]H NMR (DMSO-d_6) δ 8.6 (d, J = 2.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1 H), 8.28 (dd, = 8.7, 2.5 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1H), 8.1 (d, J = 8.7 Hz, 1H), 8.0 (dd, J = 8.4, 1.4 Hz, 1H), 3.9 (s, 3H).

EXAMPLE 255

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid (255)

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid (**255**) was prepared (100%) from 2-mercapto-benzothiazol-5-carboxylic acid (**240**) and 1,2,3-trichloro-5-nitrobenzene, obtained from Aldrich, in a similar manner as described in example 251.

^{1}H NMR (DMSO-d_6) δ 11.2 (bs, 1H), 8.6 (s, 2H), 8.31 (d, J = 1.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.94 (dd, J = 8.5, 1.4 Hz, 1H). MS (M-H) 399.

EXAMPLE 256

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (256)

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (**256**) was prepared (100%) from 2-(2,6-dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid **255** in a similar manner as described in example 254.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.6 (s, 2H), 8.33 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.95 (dd, J = 8.4, 1.6 Hz, 1H), 3.9 (s, 3H).

EXAMPLE 257

5-Chloro-2-(2-methoxy-4-nitro-phenylsulfanyl)-benzothiazole (257)

5-Chloro-2-(2-methoxy-4-nitro-phenylsulfanyl)-benzothiazole (**257**) was prepared (75%) from 2-methoxy-4-nitrobenzenethiol (**249**) and 2,5-dichlorobenzothiazole (**250**), in a similar manner as described in example 251.

^{1}H NMR (DMSO-d_6) δ 8.05 (bd, J = 8.6 Hz, 1H), 8.03 (d, J = 2.0, 1H), 7.99-7.94 (m, 3H), 7.48 (dd, J = 8.6, 2.1 Hz, 1H), 3.95 (s, 3H).

EXAMPLE 258

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (258)

To a solution of 2-mercapto-5-trifluoromethyl-benzothiazole (**239**) (470 mg, 2.0 mmol) in DMF (20 mL) was added NaH (Aldrich, 60% suspension in hexanes, 80 mg, 2.0 mmol). After the resulting mixture was stirred at ambient temperature for 20 minutes, was added 1,2,3-trichloro-5-nitrobenzene (Acros, 452 mg, 2.0 mmol). The mixture was then heated at 60 °C for 4 hours. After cooled to room temperature, the mixture was poured to water and stirred for 1 hour. The solid product was collected by

vacuum filtration to give **258** as a pale yellow solid (840 mg, 99%) which was used in the next reaction without further purification.

^{1}H NMR (DMSO-d_6) δ 8.61 (s, 2H), 8.27 (d, J = 8.4 Hz, 1H), 7.21 (br s, 1H), 7.74 (dd, J = 8.4,1.5 Hz, 1H). MS (M+H) 425.

EXAMPLE 259

1-[3-Chloro-5-nitro-2-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (259)

The title compound was prepared using the method of example **258**, starting with 5-trifluoromethyl-benzothiazole-2-thiol (**239**) (470 mg, 2.0 mmol), 1-(2,3-dichloro-5-nitro-phenyl)-ethanone (**248**) (466 mg, 2.0 mmol) and NaH (Aldrich, 60% suspension, 80 mg, 2.0 mmol) in DMF (20 mL). Compound **259** (750 mg, 87%) was obtained as a yellow solid.

^{1}H NMR (DMSO-d_6) δ 8.68 (d, J = 2.6 Hz, 1H), 8.62 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.20 (br s, 1H), 7.74 (dd, J = 8.5, 1.7 Hz, 1H), 2.65 (s, 3H). MS (M+H) 433.

EXAMPLE 260

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-6-carbonitrile (260)

The title compound was prepared using the method of example 258, starting with 2-mercapto-benzothiazole-6-carbonitrile (**241**) (960 mg, 5.0 mmol), 1,2,3-trichloro-5-nitrobenzene (Acros, 1.13 g, 5.0 mmol) and NaH (Aldrich, 60% suspension, 200 mg, 5.0 mmol) in DMF (25 mL). Compound **260** (1.9 g , 99%) was obtained as a yellow solid.

^{1}H NMR (DMSO-d_6) δ 8.61 (s, 2H), 8.58 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.88 (dd, J = 8.5, 1.8 Hz, 1H).

EXAMPLE 261

2-(2-Chloro-4-nitro-phenylsulfanyl)-benzothiazole-6-carbonitrile (261)

The title compound was prepared using the method of example 258, starting with 2-mercapto-benzothiazole-6-carbonitrile (**241**) (960 mg, 5.0 mmol), 2-chloro-1-fluoro-4-nitrobenzene (Aldrich, 878 mg, 5.0 mmol) and NaH (Aldrich, 60%

suspension, 200 mg, 5.0 mmol) in DMF (25 mL). Compound **261** (1.62 g, 93%) was obtained as a yellow solid.

^{1}H NMR (DMSO-d_6) δ 8.62 (d, J = 1.5 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.29 (dd, J = 8.6, 2.4 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.91 (dd, J = 8.5, 1.6 Hz, 1H). MS (M+H) 348.

EXAMPLE 262

2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carbonitrile (262)

The title compound was prepared using the method of example 258, starting with 2-mercapto-benzothiazole-5-carbonitrile (**243**) (960 mg, 5.0 mmol), 1,2,3-trichloro-5-nitrobenzene (Acros, 1.13 g, 5.0 mmol) and NaH (Aldrich, 60% suspension, 200 mg, 5.0 mmol) in DMF (25 mL). Compound **262** (1.9 g, 99%) was obtained as a yellow solid.

^{1}H NMR (DMSO-d_6) δ 8.62 (s, 2H), 8.38 (d, J = 1.2 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 8.4, 1.5 Hz, 1H).

EXAMPLE 263

2-(2-Chloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carbonitrile (263)

The title compound was prepared using the method of example 258, starting with 2-mercapto-benzothiazole-5-carbonitrile (**243**) (960 mg, 5.0 mmol), 2-chloro-1-fluoro-4-nitrobenzene (Aldrich, 878 mg, 5.0 mmol) and NaH (Aldrich, 60% suspension, 200 mg, 5.0 mmol) in DMF (25 mL). Compound **263** (1.60 g, 92%) was obtained as a yellow solid.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.56 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 1.2 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.29 (dd, J = 8.7, 2.5 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.85 (dd, J = 8.5, 1.5 Hz, 1H). MS (M+H) 348.

EXAMPLE 264

1-[3-Chloro-2-(5-methyl-benzothiazol-2-ylsulfanyl)-5-nitro-phenyl]-ethanone (264)

The title compound was prepared using the method of example 258, starting with 5-methyl-benzothiazole-2-thiol (**245**) (1.90 g, 10.5 mmol), 1-(2,3-dichloro-

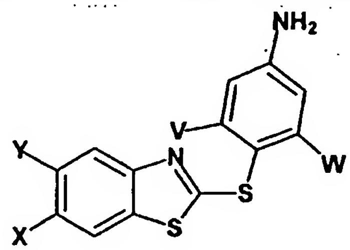
5-nitro-phenyl)-ethanone (**248**) (2.45 g, 10.5 mmol) and NaH (Aldrich, 60% suspension, 420 mg, 10.5 mmol) in DMF (20 mL). Compound **264** (3.87 g , 98%) was obtained as a yellow solid.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.65 (d, J = 2.3 Hz, 1H), 8.58 (d, J = 2.5 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.67 (br s, 1H), 7.24 (dd, J = 8.2, 1.5 Hz, 1H), 2.65 (s, 3H), 2.41 (s, 3H). MS (M+H) 379.

Examples 265-276: Reduction of the compounds of **Table 30** provides the compounds illustrated in **Table 31**

Table 31

Table 31 illustrates the structures of examples 265-276



#	X	Y	V	W	Yield
265	H	Cl	Cl	COMe	83%
266	H	CF_3	Cl	H	97%
267	H	CO_2Me	Cl	H	96%
268	H	CO_2Me	Cl	Cl	93%
269	H	Cl	H	OMe	100%
270	H	CF_3	Cl	Cl	96%
271	H	CF_3	Cl	COMe	100%
272	CN	H	Cl	Cl	98%
273	CN	H	Cl	H	93%
274	H	CN	Cl	Cl	80%
275	H	CN	Cl	H	93%
276	H	Me	Cl	COMe	68%

EXAMPLE 265

1-[5-Amino-3-chloro-2-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (265)

To a 0.14M solution of 1-[3-Chloro-2-(5-chloro-benzothiazol-2-ylsulfanyl)-5-nitro-phenyl]-ethanone (**251**)(4.08 g, 10.26 mmol) in a 2:2:1 solution of EtOH, obtained from gold shield,:THF, obtained from Aldrich,:H_2O was added $NH_4^+Cl^-$, obtained from Aldrich, (2.74 g, 51.29 mmol) followed by iron(0) powder, obtained from Aldrich, (2.86 g, 51.29 mmol). The resulting solution was heated to reflux for 2.5 h with vigorous stirring. TLC and mass spectral analysis showed starting material and hydroxyl amine intermediate so an additional 5 Eq. of both $NH_4^+Cl^-$ and iron powder were subsequently added and the reaction mixture was allowed to continue to reflux for an additional 1.75 hours. The hot solution was immediately filtered through a plug of celite and the celite was washed with copious amounts of EtOAc. The organic layer was concentrated under vaccum, resuspended in EtOAc (100 mL) and $NaHCO_3$ (100mL),and extracted 3 times with EtOAc (100 mL). The organic layer was washed twice with saturated aqueous brine (100 mL), dried over Na_2SO_4, concentrated under vacuum, and purified by column chromatography (10-50% EtOAc in hexane) to yield compound **265** (3.14 g, 83%) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ 7.95 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.39 (dd, J= 8.6, 2.1 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.41 (s, 2H), 2.45 (s, 3H). MS (M+H) 369.

EXAMPLE 266

3-Chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl amine (266)

3-Chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenylamine (**266**) was prepared (97%) from 2-(2-Chloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (**252**), in a similar manner as described in example 90.

^{1}H NMR (DMSO-d_6) δ 8.2-8.12 (m, 2 H), 7.65 (dd, J = 8.5, 1.7 Hz, 1 H), 7.52 (d, J = 8.5 Hz, 1H), 6.9 (d, J = 2.4 Hz, 1H), 6.7 (dd, J = 8.5, 2.4 Hz, 1H), 6.25 (bs, 2 H).). MS (M-H) 359.

EXAMPLE 267

2-(4-Amino-2-chloro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (267)

2-(4-Amino-2-chloro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (**267**) was prepared (96%) from 2-(2-Chloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (**254**) by the method of example 90.

^{1}H NMR (DMSO-d_6) δ 8.3 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1 H), 7.88 (dd, = 8.4, 1.6 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 8.5, 2.4 Hz, 1H), 3.9 (s, 3H). MS (M-H) 349.

EXAMPLE 268

2-(4-Amino-2,6-dichloro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester(268)

2-(4-Amino-2,6-dichloro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (**268**) was prepared (93%) from 2-(2,6-Dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carboxylic acid methyl ester (**256**) in a similar manner as described in example 90.

^{1}H NMR (DMSO-d_6) δ 8.34 (d, J = 1.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 8.4, 1.6 Hz, 1H), 6.9 (s, 2H), 6.5 (s, 2H), 3.9 (s, 3H). MS (M-H) 383.

EXAMPLE 269

4-(5-Chloro-benzothiazol-2-ylsulfanyl)-3-methoxy-phenylamine (269)

4-(5-Chloro-benzothiazol-2-ylsulfanyl)-3-methoxy-phenylamine (**269**) was prepared (100%) from 5-chloro-2-(2-methoxy-4-nitro-phenylsulfanyl)-benzothiazole (**257**), by the method of example 265.

^{1}H NMR (400MHz, DMSO-d_6) δ 7.9 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 2.0, 1H), 7.34 (dd, J = 8.5, 2.0 Hz, 1H), 7.3 (d, J = 8.3 Hz, 1H), 6.39 (d, J = 2.0 Hz, 1H), 6.29 (dd, J = 8.3, 2.1 Hz, 1H), 5.93 (s, 2H), 3.7 (s, 3H). MS (M+H) 323.

EXAMPLE 270

3,5-Dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenylamine (270)

To a solution of 2-(2,6-dichloro-4-nitro-phenylsulfanyl)-5-trifluoromethyl-benzothiazole (**258**) (840 mg, 1.98 mmol) in EtOAc (20 mL) was added tin chloride dihydrate (Aldrich, 2.15 g, 9.52 mmol) and the resulting mixture was heated to reflux for 3 hours. After cooled to room temperature, to the mixture was added excess of 4N aqueous NaOH solution and the resulting mixture was stirred for 20 minutes. The

mixture was filtered through Celite pad and washed with EtOAc. The organic layer was separated , washed twice with a brine solution, dried over Na_2SO_4, and concentrated under vacuum to give compound **270** (755 mg , 96%) product as a pale yellow solid, which was used in the next reaction without further purification.

^{1}H NMR (DMSO-d_6) δ 8.20-8.15 (m, 2H), 7.66 (dd, J = 8.4,1.7 Hz, 1H), 6.88 (s, 2H), 6.50 (s, 2H). MS (M+H) 395.

EXAMPLE 271

1-[5-Amino-3-chloro-2-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (271)

The title compound was prepared using the method of example 270, starting with 1-[3-chloro-5-nitro-2-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (**259**) (750 mg, 1,67 mmol), tin chloride dihydrate (Aldrich, 1.89 g, 8.37 mmol). Compound **271** (755 mg, 100%) was obtained as a yellowish solid.

^{1}H NMR (DMSO-d_6) δ 8.20-8.13 (m, 2H), 7.66 (dd, J = 8.4, 1.0 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.43 (s, 2H), 2.48 (s, 3H). MS (M+H) 403.

EXAMPLE 272

2-(4-Amino-2,6-dichloro-phenylsulfanyl)-benzothiazole-6-carbonitrile (272)

The title compound was prepared using the method of example 270, starting with 2-(2,6-dichloro-4-nitro-phenylsulfanyl)-benzothiazole-6-carbonitrile (**260**) (1.9 g, 4.97 mmol), tin chloride dihydrate (Aldrich, 5.62 g, 24.9 mmol). Compound **272** (1.72 g , 98%) was obtained as a yellowish solid.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.48 (d, J = 1.5 Hz,1H), 7.97 (d, J = 8.7 Hz, 1H), 7.86 (dd, J = 8.5, 1.7 Hz, 1H), 6.88 (s, 2H), 6.53 (s, 2H). MS (M+H) 352.

EXAMPLE 273

2-(4-Amino-2-chloro-phenylsulfanyl)-benzothiazole-6-carbonitrile (273)

The title compound was prepared using the method of example 270, starting with 2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazole-6-carbonitrile (**261**) (1.6

g, 4.6 mmol), tin chloride dihydrate (Aldrich, 5.21 g, 23.1 mmol). Compound **273** (1.36 g, 93%) was obtained as a yellowish solid.

MS (M+H) 318

EXAMPLE 274

2-(4-Amino-2,6-dichloro-phenylsulfanyl)-benzothiazole-5-carbonitrile (274)

The title compound was prepared using the method of example 270, starting with 2-(2,6-dichloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carbonitrile (**262**) (1.9 g, 4.97 mmol), tin chloride dihydrate (Aldrich, 5.62 g, 24.9 mmol). Compound **274** (1.40 g, 80%) was obtained as a yellowish solid.

^{1}H NMR (DMSO-d_6) δ 8.35 (d, J = 1.4 Hz,1H), 8.16 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 8.4, 1.5 Hz, 1H), 6.88 (s, 2H), 6.50 (s, 2H). MS (M+H) 352.

EXAMPLE 275

2-(4-Amino-2-chloro-phenylsulfanyl)-benzothiazole-5-carbonitrile (275)

The title compound was prepared using the method of example 270, starting with 2-(2-chloro-4-nitro-phenylsulfanyl)-benzothiazole-5-carbonitrile (**263**) (1.59 g, 4.58 mmol), tin chloride dihydrate (Aldrich, 5.18 g, 22.9 mmol). Compound **275** (1.35 g, 93%) was obtained as a yellowish solid.

^{1}H NMR (DMSO-d_6) δ 8.32 (d, J = 1.4 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.71 (dd, J = 8.3, 1.5 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 8.4, 2.4 Hz, 1H). MS (M+H) 318.

EXAMPLE 276

1-[5-Amino-3-chloro-2-(5-methyl-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (276)

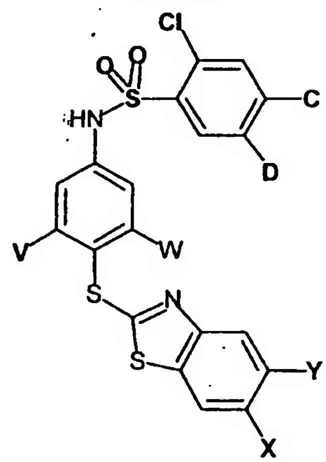
To a solution of 1-[3-chloro-5-nitro-2-(5-methyl-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone (**264**) (3.87 g, 10.2 mmol) in 2:2:1 of EtOH/THF/H_2O, was added ammonium chloride (Aldrich 2.74 g, 51.2 mmol) and iron powder (Aldrich, 2.87 g, 51.2 mmol). The mixture was refluxed for 3 hours. The mixture was filtered through Celite pad while it was hot, washed the Celite pad with EtOAc. The filtrate was diluted with saturated aqueous $NaHCO_3$ solution and was extracted 3x with EtOAc (150 mL).

The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was chromatographed (0-15% EtOAc in CH_2Cl_2) to yield 2.42 g (68%) of compound **276** as a pale yellow solid.

^1H NMR (DMSO-d_6) δ 8.10 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 1.1 Hz, 1H), 7.16 (dd, J = 8.1, 1.2 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.69 (d, J = 2.5 Hz, 1H), 6.38 (s, 2H), 2.46 (s, 3H), 2.40 (s, 3H). MS (M+H) 349.

Examples 277-307: The compounds illustrated in **Table 32** were prepared by sulfonylation of the anilines of **Table 31** by the method of Example 277 unless otherwise specified.

Table 32



Example #	C	D	V	W	X	Y	MS(M-H)	Yield
277	CF_3	H	COMe	Cl	H	Cl	609	72%
278	Cl	H	COMe	Cl	H	Cl	575	39%
279	Cl	Me	COMe	Cl	H	Cl	589	73%
280	Cl	H	H	Cl	H	CF_3	567	68%
281	CF_3	H	H	Cl	H	CF_3	601	70%
282	Cl	H	H	Cl	H	CO_2Me	557	68%
283	Cl	H	Cl	Cl	H	CO_2Me	557	68%
284	CF_3	H	H	Cl	$CONH_2$	H	576	14%
285	CF_3	H	Cl	Cl	$CONH_2$	H	610	55%

286	CF_3	H	H	Cl	CN_4H	H	601	67%
287	CF_3	H	Cl	Cl	CN_4H	H	635	65%
288	CF_3	H	H	OMe	H	Cl	563	72%
289	Cl	H	Cl	Cl	H	CF_3	601	61%
290	CF_3	H	Cl	Cl	H	CF_3	635	76%
291	Cl	H	COMe	Cl	H	CF_3	609	32%
292	CF_3	H	COMe	Cl	H	CF_3	643	29%
293	Cl	H	Cl	Cl	CN	H	558	71%
294	CF_3	H	Cl	Cl	CN	H	592	83%
295	Cl	H	H	Cl	CN	H	524	88%
296	CF_3	H	H	Cl	CN	H	558	64%
297	Cl	H	Cl	Cl	H	CN	558	66%
298	CF_3	H	Cl	Cl	H	CN	592	72%
299	Cl	H	H	Cl	H	CN	524	58%
300	CF_3	H	H	Cl	H	CN	558	58%
301	Cl	H	Cl	Cl	H	CN_4H	601	77%
302	CF_3	H	Cl	Cl	H	CN_4H	635	82%
303	Cl	H	Cl	Cl	H	$CONH_2$	601	77%
304	Cl	H	H	Cl	H	CN_4H	567	78%
305	CF_3	H	H	Cl	H	CN_4H	601	83%
306	CF_3	H	COMe	Cl	H	Me	589	73%
307	Cl	Me	COMe	Cl	H	Me	569	74%

EXAMPLE 277

N-[3-Acetyl-5-chloro-4-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-2-chloro-4-trifluoromethyl-benzenesulfonamide (277)

To a 1M solution of 1-[5-Amino-3-chloro-2-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-ethanone, (265) (4.12 g, 11.19 mmol) in pyridine, obtained from Aldrich, was added 2-chloro-4-trifluoromethyl-benzenesulfonyl chloride (3.75 g, 13.43 mmol) and heated to 90 °C for 1.5 hours. The crude reaction mixture was concentrated under vacuum, partitioned between 2M aqueous HCl (100 mL) and EtOAc (100 mL), and extracted 3 times with EtOAc (100 mL). The combined organic layers were washed twice with saturated aqueous brine (100 mL), dried over Na_2SO_4, concentrated under vacuum, purified by column chromatography (0-5% Et_2O in CH_2Cl_2), and triturated with

CH_2Cl_2/hexane mixture with 0.5 mL of MeOH added to yield compound **277** (4.9 g, 72%) as an off white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ 11.9 (s, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.23 (s, 1H), 8.01 (bd, J = 7.2 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.9 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.6, 2.1 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 2.45 (s, 3H). MS (EI): *m/z* 609 (38, M-H), 610 (10, M-H), 611 (50, M-H), 612 (12, M-H), 613 (20, M-H), 614 (5, M-H), 615 (3, M-H).

EXAMPLE 278

N-[3-Acety-5-chloro-4-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-2,4-dichloro-benzenesulfonamide (278) By the method of example 93.

^{1}H NMR (DMSO-d_6) δ 11.8 (s, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.1-7.95 (m, 2 H), 7.91 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 8.6, 2.1 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.6, 2.1 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 2.45 (s, 3H). MS (M-H) 575.

EXAMPLE 279

N-[3-Acetyl-5-chloro-4-(5-chloro-benzothiazol-2-ylsulfanyl)-phenyl]-2,4-dichloro-5-methyl-benzenesulfonamide(279)

^{1}H NMR (DMSO-d_6) δ 11.8 (s, 1H), 8.3 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.93-7.9 (m, 2H), 7.46 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.6, 2.1 Hz, 1H), 7.3 (d, J = 2.4 Hz, 1H), 2.45 (s, 3H), 2.4 (s, 3H). MS (M-H) 589.

EXAMPLE 280

2,4-Dichloro-N-[3-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (280)

^{1}H NMR (400MHz, DMSO-d_6) δ 11.6 (s, 1 H), 8.23-8.16 (m, 3 H), 7.96 (bs, 1 H), 7.88 (bd, J = 8.6 Hz, 1H), 7.75-7.67 (m, 2 H), 7.4 (bs, 1H), 7.23 (bd, J = 10.7 Hz, 1 H). MS M-H) 567.

EXAMPLE 281

2-Chloro-N-[3-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (281)

^{1}H NMR (400MHz, DMSO-d_6) δ 11.8 (s, 1 H), 8.4 (d, J = 8.3 Hz, 1 H), 8.23 (bs, 1 H), 7.98-7.94 (m, 2 H), 8.03 (bd, J = 8.4 Hz, 1 H), 7.9 (d, J = 8.6 Hz, 1H), 7.69 (bd, J = 10.1 Hz, 1 H), 7.44 (d, J = 2.4 Hz, 1 H), 7.25 (dd, J = 8.5, 2.4 Hz, 1 H). MS (M-H) 601.

EXAMPLE 282

2-[2-Chloro-4-(2,4-dichloro-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-5-carboxylic acid methyl ester(282)

^{1}H NMR (DMSO-d_6) δ 11.5 (s, 1H), 8.32 (d, J = 1.5 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1 H), 8.08 (d, = 8.4 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 9.1, 1.6 Hz, 1 H), 7.88 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 8.6, 2.1 Hz, 1H), 7.4 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.2, 2.0 Hz, 1 H), 3.9 (s, 3H). MS (M-H) 557.

EXAMPLE 283

2-[2,6-Dichloro-4-(2,4-dichloro-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-5-carboxylic acid methyl ester(283) By the method of example 93.

^{1}H NMR (DMSO-d_6) δ 11.9 (s, 1H), 8.32 (d, J = 0.9 Hz, 1H), 8.22 (d, J = 8.6 Hz, 1 H), 8.09 (d, = 8.4 Hz, 1H), 8.0 (d, J = 1.9 Hz, 1H), 7.92 (dd, J = 8.4, 1.6 Hz, 1 H), 7.75 (dd, J = 8.6, 2.1 Hz, 1H), 7.4 (s, 2H), 3.9 (s, 3H). MS (M-H) 591.

EXAMPLE 284

2-[2-Chloro-4-(2-chloro-4-trifluoromethyl-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-6-carboxylic acid amide (284)

2-[2-Chloro-4-(2-chloro-4-trifluoromethyl-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-6-carboxylic acid amide (284) was prepared (14%) from 2-chloro-N-[3-chloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (296) by the method of example 303.

^{1}H NMR (DMSO-d_6) δ 11.8 (s, 1H), 8.42 (d, J = 1.3 Hz, 1H), 8.38 (d, J = 8.5 Hz, 1 H), 8.21 (bs, 1H), 8.05-7.99 (m, 2H), 7.94 (dd, J = 8.6, 1.5 Hz, 1 H), 7.89-7.83 (m, 2H), 7.45 (s, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.24 (dd, J = 8.5, 2.1 Hz, 1H). MS (M-H) 576.

EXAMPLE 285

2-[2,6-Dichloro-4-(2-chloro-4-trifluoromethyl-benzensulfonylamino)-phenylsulfanyl]-benzothiazole-6-carboxylic acid amide (285)

2-[2,6-Dichloro-4-(2-chloro-4-trifluoromethyl-benzensulfonylamino)-phenylsulfanyl]-benzothiazole-6-carboxylic acid amide (285) was prepared (55%) from 2-chloro-N-[3,5-dichloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (294), by the method of example 303.

^{1}H NMR (DMSO-d_6) δ 12.0 (bs, 1H), 8.48-8.4 (m, 2H), 8.23 (bs, 1H), 8.05-8.0 (m, 2H), 7.95 (dd, J = 8.5, 1.7 Hz, 1 H), 7.85 (d, J = 8.5 Hz, 1H), 7.48 (s, 1H), 7.4 (s, 2H). MS (M-H) 610.

EXAMPLE 286

2-Chloro-N-{3-chloro-4-[6-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide

2-Chloro-N-{3-chloro-4-[6-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (286) was prepared (67%) from 2-chloro-N-[3-chloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (296)), by the method of example 301.

^{1}H NMR (DMSO-d_6) δ 8.62 (bs, 1H), 8.36 (d, J = 8.5 Hz, 1H), 8.19 (bs, 1H), 8.08 (d, J = 8.1 Hz, 1H), 8.04-7.95 (m, 2H), 7.84 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.2 (dd, J = 7.9, 1.8 Hz, 1H). MS (M-H) 601.

EXAMPLE 287

2-Chloro-N-{3,5-dichloro-4-[6-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (287)

2-Chloro-N-{3,5-dichloro-4-[6-(1H-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (287) was prepared (65%) from 2-chloro-N-[3,5-dichloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (294) by the method of example 301.

^{1}H NMR (DMSO-d_6) δ 8.65 (bs, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.24 (bs, 1H), 8.09 (d, J = 8.6 Hz, 1 H), 8.06-7.98 (m, 2H), 7.4 (bs, 2H). MS (M-H) 635.

EXAMPLE 288

2-Chloro-N-[4-(5-chloro-benzothiazol-2-ylsulfanyl)-3-methoxy-phenyl]-4-trifluoromethyl-benzenesulfonamide (288) By the method of example 93.

^{1}H NMR (DMSO-d_6) δ 11.5 (s, 1H), 8.4 (d, J = 8.3 Hz, 1H), 8.2 (bs, 1H), 8.01 (d, J = 8.3, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.6, 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.83 (dd, J = 8.4, 2.1 Hz, 1H), 3.8 (s, 3H). MS (M-H) 563.

EXAMPLE 289

2,4-Dichloro-*N*-[3,5-dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (289)

^{1}H NMR (DMSO-d_6) δ 11.90 (s, 1H), 8.25-8.15 (m, 3H), 7.98 (d, J = 2.0 Hz, 1H), 7.76-7.67 (m, 2H), 7.38 (s, 2H). MS (M-H) 601

EXAMPLE 290

2-Chloro-*N*-[3,5-dichloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (290)

^{1}H NMR (DMSO-d_6) δ 11.90 (br s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.26-8.15 (m, 3H), 8.03 (dd, J = 8.4, 1.7 Hz, 1H), 7.68 (dd, J = 8.6, 1.6 Hz, 1H), 7.40 (s, 2H). MS (M-H) 635.

EXAMPLE 291

***N*-[3-Acetyl-5-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-2,4-dichloro-benzenesulfonamide (291)**

^{1}H NMR (DMSO-d_6) δ 11.80 (br s, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.22-8.15 (m, 2H), 7.97 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 8.6, 2.1 Hz, 1H), 7.69 (dd, J = 8.6, 1.6 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 2.47 (s, 3H). MS (M-H) 609.

EXAMPLE 292

***N*-[3-Acetyl-5-chloro-4-(5-trifluoromethyl-benzothiazol-2-ylsulfanyl)-phenyl]-2-chloro-4-trifluoromethyl-benzenesulfonamide (292)**

^{1}H NMR (DMSO-d_6) δ 11.90 (br s, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.23-8.17 (m, 3H), 8.01 (dd, J = 8.5, 1.4 Hz, 1H), 7.65 (dd, J = 8.5, 1. 5 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 2.48 (s, 3H). MS (M-H) 643.

EXAMPLE 293

2,4-Dichloro-*N*-[3,5-dichloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (293)

^{1}H NMR (DMSO-d_6) δ 11.90 (br s, 1H), 8.49 (d, J = 1.1 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.86 (dd, J = 8.5, 1.6 Hz, 1H), 7.74 (dd, J = 8.6, 2.0 Hz, 1H), 7.38 (s, 2H). MS (M-H) 558.

EXAMPLE 294

2-Chloro-*N*-[3,5-dichloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (294)

^{1}H NMR (DMSO-d_6) δ 11.90 (br s, 1H), 8.49 (d, J = 1.5 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.24 (br s, 1H), 8.03 (dd, J = 8.2, 1.0 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 8.5, 1.7 Hz, 1H), 7.40 (s, 2H). MS (M-H) 592.

EXAMPLE 295

2,4-Dichloro-*N*-[3-chloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (295)

^{1}H NMR (DMSO-d_6) δ 11.60 (br s, 1H), 8.49 (d, J = 1.8 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.00-7.94 (m, 2H), 7.90-7.84 (m, 2H), 7.72 (dd, J = 8.6, 2.0 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.5, 2.4 Hz, 1H). MS (M-H) 524.

EXAMPLE 296

2-Chloro-*N*-[3-chloro-4-(6-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (296)

^{1}H NMR (DMSO-d_6) δ 11.78 (br s, 1H), 8.48 (br s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.22 (br s, 1H), 8.02 (br d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.86 (dd, J = 8.5, 1.5 Hz, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = 8.5, 2.4 Hz, 1H). MS (M-H) 558.

EXAMPLE 297

2,4-Dichloro-*N*-[3,5-dichloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (297)

^{1}H NMR (DMSO-d_6) δ 11.90 (br s, 1H), 8.36 (d, J = 1.1 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 8.5, 1.5 Hz, 1H), 7.73 (dd, J = 8.4, 2.0 Hz, 1H), 7.38 (s, 2H). MS (M-H) 558.

EXAMPLE 298

2-Chloro-*N*-[3,5-dichloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (298)

^{1}H NMR (DMSO-d_6) δ 11.98 (br s, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.35 (d, J = 1.5 Hz, 1H), 8.23 (br s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.03 (dd, J = 8.4, 1.0 Hz, 1H), 7.76 (dd, J = 8.4, 1.4 Hz, 1H), 7.40 (s, 2H). MS (M-H) 592.

EXAMPLE 299

2,4-Dichloro-*N*-[3-chloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide

^{1}H NMR (DMSO-d_6) δ 11.60 (br s, 1H), 8.36 (d, J = 1.5 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.75 (dd, J = 8.4, 1.5 Hz, 1H), 7.72 (dd, J = 8.5, 2.0 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.5, 2.4 Hz, 1H). MS (M-H) 524.

EXAMPLE 300

2-Chloro-*N*-[3-chloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (300)

^{1}H NMR (DMSO-d_6) δ 11.70 (br s, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 1.4 Hz, 1H), 8.21 (br s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 8.5, 1.5 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.75 (dd, J = 8.4, 1.6 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.5, 2.4 Hz, 1H). MS (M-H) 558.

EXAMPLE 301

2,4-Dichloro-*N*-{3,5-dichloro-4-[5-(1*H*-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-benzenesulfonamide (301)

To a solution of 2,4-dichloro-*N*-[3,5-dichloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (**297**) (250 mg, 0.45 mmol) in toluene (5 mL), was added azidotrimethylsilane (Aldrich, 0.12 mL, 0.90 mmol) and dibutyltin oxide (Aldrich, 11 mg, 0.045 mmol). The resulting mixture was heated at 90 °C overnight (15 hours). A 1M aqueous solution of HCl (50 mL) and ice was added and the crude reaction mixture was extracted 3x with EtOAc (50 mL). The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was chromatographed (20% EtOAc in CH_2Cl_2, then 10% MeOH in CH_2Cl_2) to yield 209 mg (77%) of product as a white solid.

^{1}H NMR (DMSO-d$_6$) δ 8.44 (d, J = 1.7 Hz, 1H), 8.21 (d, J = 8.6 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.01 (dd, J = 8.4, 1.7 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.6, 2.0 Hz, 1H), 7.38 (s, 2H). MS (M-H) 601.

EXAMPLE 302

2-Chloro-*N*-{3,5-dichloro-4-[5-(1*H*-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (302)

The title compound was prepared by the method of example 301.

^{1}H NMR (DMSO-d$_6$) δ 8.44 (d, J = 1.5 Hz, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 1.3 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 8.4, 1.4 Hz, 1H), 7.40 (s, 2H). MS (M-H) 635.

EXAMPLE 303

2-[2,6-Dichloro-4-(2,4-dichloro-benzenesulfonylamino)-phenylsulfanyl]-benzothiazole-5-carboxylic acid amide (303)

To a solution of 2,4-dichloro-*N*-[3,5-dichloro-4-(5-cyano-benzothiazol-2-ylsulfanyl)-phenyl]-benzenesulfonamide (297) (250 mg, 0.45 mmol) in *tert*-butanol (10 mL), was added KOH (EM Science Product, 126 mg, 2.25 mmol). The resulting mixture was refluxed for 1 hour. After cooling to room temperature, a 1M aqueous solution of HCl (50 mL) was added and the crude reaction mixture was extracted 3x with EtOAc (50 mL). The organic layers were combined and washed twice with a brine solution (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude solid was chromatographed (20% EtOAc in CH_2Cl_2, then 10% MeOH in CH_2Cl_2) to yield 207 mg (80%) of compound **303** as a white solid.

^{1}H NMR (DMSO-d_6) δ 11.80 (s, 1H), 8.33 (br s, 1H), 8.22 (dd, J = 8.5, 1.9 Hz, 1H), 8.08 (br s, 1H), 8.03-7.96 (m, 2H), 7.85 (m, 1H), 7.74 (m, 1H), 7.47 (br s, 1H), 7.38 (s, 2H). MS (M-H) 578.

EXAMPLE 304

2,4-Dichloro-*N*-{3-chloro-4-[5-(1*H*-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-benzenesulfonamide (304) The title compound was prepared by the method of example 301.

^{1}H NMR (DMSO-d_6) δ 8.44 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.01 (dd, J = 8.4, 1.6 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.71 (dd, J = 8.6, 2.1 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 8.6, 2.4 Hz, 1H). MS (M-H) 567.

EXAMPLE 305

2-Chloro-*N*-{3-chloro-4-[5-(1*H*-tetrazol-5-yl)-benzothiazol-2-ylsulfanyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (305).

The title compound was prepared by the method of example 301.

^{1}H NMR (DMSO-d_6) δ 8.43 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 1.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.03-7.96 (m, 2H), 7.85 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 8.6, 2.4 Hz, 1H). MS (M-H) 601.

EXAMPLE 306

***N*-[3-Acetyl-5-chloro-4-(5-methyl-benzothiazol-2-ylsulfanyl)-phenyl]-2-chloro-4-trifluoromethyl-benzenesulfonamide (306).**

^{1}H NMR (DMSO-d_6) δ 11.90 (br s, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.23 (d, J = 1.2 Hz, 1H), 8.01 (dd, J = 8.4, 1.1 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.19 (dd, J = 8.5, 1.2 Hz, 1H), 2.47 (s, 3H), 2.40 (s, 3H). MS (M-H) 589.

EXAMPLE 307

***N*-[3-Acetyl-5-chloro-4-(5-methyl-benzothiazol-2-ylsulfanyl)-phenyl]-2,4-dichloro-5-methyl-benzenesulfonamide (307)**

^{1}H NMR (DMSO-d_6) δ 11.70 (br s, 1H), 8.28 (s, 1H), 7.92 (s, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.64 (s, 1H), 7.45 (d, J = 2.3 Hz, 1H), 7.29 (d, J = 2.3 Hz, 1H), 7.19 (dd, J = 8.2, 1.5 Hz, 1H), 2.48-2.38 (m, 9H). MS (M-H) 569.

EXAMPLE 308

3-Hydroxy-6-methylquinoline (308)

A solution of 3-Amino-6-methylquinoline [(1.21g, 7.65mmol), prepared according to J.Chem.Soc.2024-2027(1948) Morley, J. S.; Simpson, J. C. E.] in 6N H_2SO_4 (25ml) was cooled in an ice bath. To the solution $NaNO_2$ (560mg, 8.10mmol) in water (2ml) was added and stirred for 30min at 0 degrees. Separately 5% H_2SO_4 was refluxed and above Diazo reaction mixture was added to this refluxing solution. After 30min the reaction mixture was cooled to room temperature, and was neutralized by 6N NaOH. The resulting insoluble material was collected by filtration. This solid was recrystallized by $CHCl_3$/AcOEt to afford compound (**308**) (348mg, 29%).

^{1}H NMR (300MHz,DMSO-d_6) δ 7.34 (1H, dd, J=1.9, 8.6Hz), 7.42(1H, d, J=2.8Hz), 7.55 (1H, s), 7.79 (1H, d, J=8.6Hz), 8.50 (1H, d, J=2.8Hz).

EXAMPLE 309

3-(2,6-Dichloro-4-nitro-phenoxy)-6-methyl-quinoline (309)

To a solution of 3-Hydroxy-6-methylquinoline (**308**) (348mg, 2.19mmol) in DMF (3.5ml), was added NaH (60% oil suspension, 90mg, 2.25mmol) in one portion at room temperature. After 5min 3,4,5-Trichloronitorobenzene (509mg, 2.25mmol) in DMF (2ml) was added and the reaction mixture was heated at 50 degrees with stirring for 2hr. After cooling to room temperature. Ice/water was added to the reaction mixture, which was then acidified with 2N HCl and extracted twice with AcOEt. Organic layer was washed with Brine, dried over anhydrous $MgSO_4$, and concentrated. Crude residue was purified by column chromatography (Hexane/AcOEt=4/1, 80g of silica gel) to afford compound **309** (510mg, 67%).

^{1}H NMR (300MHz,DMSO-d_6) δ 7.52-7.57(2H,m), 7.61 (1H, s), 7.94(1H, d, J=8.6Hz), 8.63 (2H, s), 8.86 (1H, d, J=2.9Hz).

EXAMPLE 310

3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-6-carboxylic acid (310).

A solution of 3-(2,6-Dichloro-4-nitro-phnoxy)-6-methyl-quinoline(309) (510mg, 1.46mmol) and chromium (VI) oxide (292mg, 2.92mmol) in c H_2SO_4/ H_2O =2.4ml/4.7ml was heated at 100 degrees while three 292mg portions of chromic anhydride were added eight hour intervals. After 32hr heating was stopped and allowed to stand for over night. Insoluble material was collected by filtration, and this solid was washed with water twice to afford compound (310)(443mg, 80%).

^{1}H NMR (300MHz,DMSO-d_6) δ 7.94 (1H, d, J=3.0Hz), 8.14(2H, s), 8.56 (1H, s), 8.65 (2H, s), 9.09 (1H, d, J=3.0Hz).

EXAMPLE 311

3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-6-carboxylic acid methyl ester (311)

To a solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-6-carboxylic acid (310) (443mg, 0.93mmol) in dry THF (20ml) was added CH_2N_2 in Et_2O solution [Prepared from Nitrosomethylurea (1.65g) and 50%KOH (5ml)]. This mixture was stirred at room temperature for 1hr. AcOH (1ml) was added to the reaction mixture, which was then concentrated. Sat $NaHCO_3$ was added to the residue, which was extracted twice with AcOEt. Organic layer was washed by Brine, dried over anhydrous $MgSO_4$, and concentrated to afford compound **311** (415mg).

^{1}H NMR (300MHz,DMSO-d_6) δ 3.89 (3H, s), 5.75(2H, br s), 6.76 (2H, s), 7.73 (1H, d, J=2.9Hz), 8.09 (2H, s), 8.67 (1H, s), 8.94 (1H, d, J=2.9Hz).

EXAMPLE 312

3-(4-Amino-2, 6-dichloro-phenoxy)-quinoline-6-carboxylic acid methyl ester (312)

To a solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-6-carboxylic acid methyl ester **(311)** (0.93mmol) and NH_4Cl (283mg, 5.3mmol) in EtOH/THF/water (8ml/16ml/1ml)was added Iron powder (296mg, 5.3mmol). The reaction mixture was refluxed for 4hr. Insoluble materials were removed by Celite pad, which was washed by THF, acetone and then EtOH. The filtrate was concentrated, and sat $NaHCO_3$ was added and extracted twice with AcOEt. Organic layer was washed by brine, dried over anhydrous $MgSO_4$, and concentrated to afford compound **312** (372mg, over weight).

Schering-Plough Research Institute

To:	Dr. Pickett	**Date:**	July 22, 2002
From:	Dr. Roehl and Dr. Chatterjee	**Copies:**	Distribution
Subject:	Actions from 7/12/02 Staff Meeting		
Reference:	CB2 inverse agonist, TACE inhibitor, IGFR		

CB2 inverse agonist program

SCH 414319, a selective CB2 inverse agonist, was selected for toxicology studies in May '01. Drs. Mirro and Kozlowski provided updates on preliminary results of the toxicology studies and on the backup program.

The most significant finding in the toxicology program was mortality at high doses in 3 month rat and monkey studies. Deaths were seen at 33 days and histopathological evaluation of unscheduled sacrifices and found deads failed to demonstrate a cause of death. Clinical pathology findings included decreased body weight gain and body weight loss in rats, and decreased lymphocytes, elevated liver enzymes, and electrolyte changes in rats and monkeys. Estimated exposure multiples at the no effect dose in rats (15 mg/kg, po) and monkeys (4 mg/kg, po) were 15x and 6x, respectively, based on AUC and 106x and 50x, respectively, based on C_{max}. There were no mortalities in 2 week studies. There is insufficient information at present to ascribe a mechanism-based explanation for the mortalities. Although there appears to be no early evidence for immune involvement, plans are to examine monkeys for signs of CB2-dependent immune activation, e.g., increased activation markers in leukocytes and increased cytokine levels in plasma. In addition, studies will be conducted to investigate whether chronic inverse agonist administration is associated with increased CB2 receptor density and/or sensitivity to ligands. Finally, a 2 week accelerated toxicity model (high doses, administered bid) will be explored to look for potential surrogate markers of toxicity and for screening of potential backup candidates.

Efforts are underway in Chemistry to make significant structural changes to SCH 414319 to identify structurally diverse analogs with equal or better in vitro profiles and better exposure multiples. Analogs with high CB2 receptor affinity, e.g., SCH 471826, SCH 491673, and SCH 515552, will be characterized to determine if a replacement presently exists. Group plans were accepted.

<u>**Action**</u>

- Safety Pharmacology group to be consulted to design a study(ies) to determine whether there is a functional effect of binding to the calcium channel that might have contributed to the mortality observed in the 3-month toxicity studies.

TACE inhibitor

The objective of the program is to identify an inhibitor of the TNFα converting enzyme, leading to lowering of circulating TNFα, as a treatment for inflammatory diseases such as rheumatoid arthritis. Dr. Niu reviewed the screening program and TACE biology. Several compounds with pM potency and good selectivity have been isolated, including SCH617439 and SCH615050. Since processing of TACE takes place intracellularly, a standard human whole blood assay has been used to measure potency, however, compounds have shown significant loss of potency (>1000X), similarly to TACE inhibitors reported by other companies. A serum-free PBMC assay showed excellent penetration with SCH615024 but not other compounds. Addition of BSA and plasma increase the Ki of all compounds. Thus protein binding and cell penetration account for some but not all of the loss of potency in the whole blood cell assay. Pharmacokinetics and supporting data with other assays are being examined to address the potency issue.

Dr. Lavey summarized the chemistry effort and included competitive programs. A BMS/DuPont compound is most advanced in Phase II trials. Other companies (Wyeth, Novartis, Pfizer, Roche, Wakunaga, Astra-Zeneca, British Biotech, Darwin Discovery, Glaxo-SKB, Shionogi) have discovery stage TACE programs. Lead compounds contain a novel cyclopropyl amide moiety. SAR shows that the hydroxamic acid group is essential for *in vivo* potency in this series. X-ray crystal structures indicate that lead compounds, as well as the DuPont lead compound, exhibit binding to the enzyme active site. Current efforts have focused on modifications to the amide, central aromatic ring, and quinoline tail to improve Ki, physical properties and cellular affinity.

__Actions__
- No actions were identified.

IGFR

The objective of the program is to generate monoclonal antibodies specific for the IGFR1 receptor, necessary for cell transformation, as a treatment for cancers. Dr. Wang described the biology program. IGFR1 and its ligand (IGF-II) are overexpressed in some human tumors, and elevated serum IGF-I is a risk factor for several major cancer types. Mouse neutralizing anti-IGFR1 antibodies have been shown to inhibit anchorage-independent cell growth and growth of xenografts in athymic mice. The Medarex-derived human anti-IGFR1 antibody 19D12 was isolated, genetically cloned and sequenced and shown to inhibit human colon cancer xenograft growth in mice (37% inhibition). Antibody 19D12 is being further characterized in additional xenograft models to determine correlation of receptor and ligand expression with antibody efficacy. The antibody will also be tested *in vivo* in combination with Herceptin, Iressa and other drugs.

Dr. Greenberg summarized the production and purification of 400 mg of the 19D12 antibody in Wave Reactors for *in vivo* proof-of-principle studies and current efforts to construct a high expression CHO DXB11 cell line for the antibody. Current yield of 19D12 in CHO cells is 5-20 mg/L. In addition, modifications to the unusual amino acids present in heavy and light chain variable framework regions of 19D12 have been made at DNAX and BiotechDev. The modified antibodies were shown to be biologically active.

__Actions__
- **Team** to discuss with Clinical Oncology other drugs for possible combination studies.

^{1}H NMR (300MHz,DMSO-d_6) δ 3.89 (3H, s), 5.75(2H,s), 6.76 (2H, s), 7.73 (1H, d, J=2.9Hz), 8.09 (2H, s), 8.67 (1H, s), 8.94 (1H, d, J=2.9Hz).

EXAMPLE 313

3-Hydroxy-8-quinolinecarboxylic acid methyl ester (313)

To the mixture of 8-Quinoline carboxylic acid (500mg, 2.89mmol) in THF (80ml) was added CH_2N_2 in Et_2O sol. [Prepared from Nitrosomethylurea (1.65g) and 50%KOH (5ml)] at room temperature. The reaction mixture was stirred for 12 hr and then concentrated to give the intermediate ester.

^{1}H NMR (300MHz,DMSO-d_6) δ 3.92 (3H, s), 7.60-7.70 (2H, m), 7.93-7.96(1H, m), 8.14-8.17 (1H, m), 8.44-8.48(1H, m), 8.97-8.99(1H, m)

To a solution of the intermediate 8-Quinolinecarboxylic acid methyl ester (2.89mmol) in AcOH (4ml) was added 30% H_2O_2 (0.6ml). The reaction mixture was heated at 85 degrees for 7.5hr. The reaction mixture was treated with sat $NaHCO_3$, and extracted six times with $CHCl_3$. Organic layer was dried over anhydrous $MgSO_4$, and concentrated. Crude residue was triturated with $CHCl_3$/Toluene to provide compound **313** (256mg, 44%, in 2 steps).

^{1}H NMR (300MHz,DMSO-d_6) δ 3.89 (3H, s), 7.52(1H, d, J=6.9Hz), 7.57 (1H, d, J=1.5Hz), 7.66 (1H, dd, J=1.5, 6.9Hz), 7.95 (1H, dd, J=1.5, 8.1Hz), 8.63 (1H, d, J=2.7Hz), 10.5 (1H, br s).

EXAMPLE 314

3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-8-carboxylic acid methyl ester (314)

To a solution of 3-Hydroxy-8-quinolinecarboxylic acid methyl ester (**313**) (256mg, 1.26mmol) and 3,4,5-Trichloronitrobenzene (294mg, 1.30mmol) in Acetone (40ml) was added K_2CO_3 (870mg, 6.30mmol). This mixture was refluxed for 3.5hr. The reaction mixture was cooled to room temperature and insoluble materials were removed by Celite filtration. The filtrate was concentrated and the residue was purified by column chromatography. (Hexane/AcOEt=4/1, 80g of silica gel) to afford compound **314**.

^{1}H NMR (300MHz,DMSO-d_6) δ 3.92 (3H, s), 7.67(1H, dd, J=7.3Hz), 7.79 (1H, d, J=2.9Hz), 7.88 (1H, dd, J=1.5, 7.3Hz), 9.05 (1H, d, J=2.9Hz).

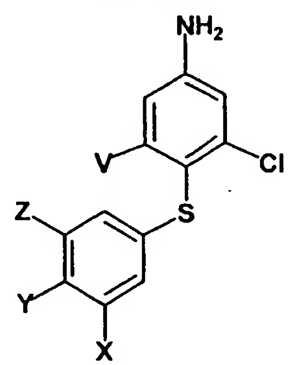
EXAMPLE 315

3-(4-Amino-2, 6-dichloro-phenoxy)-quinoline-8-carboxylic acid methyl ester(315).

To a solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-quinoline-8-carboxylic acid methyl ester **(314)** (1.26mmol) and NH_4Cl (370mg, 6.91mmol) in EtOH/THF/ H_2O =8ml/4ml/2ml was added Iron powder (386mg, 6.91mmol). The reaction mixture was.refluxed for 3.5hr. After cooling to room temperature and insoluble materials were filtered by Celite filtration. The filtrate was concentrated and sat $NaHCO_3$ was added to the residue, which was extracted twice with AcOEt. Organic layer was washed by Brine, dried over $MgSO_4$, and concentrated. Crude residue was purified by column chromatography (Hexane/AcOEt=2/1, 80g of silica gel) to afford compound **315** (543mg).

^1H NMR (300MHz,DMSO-d_6) δ 3.91(3H, s), 5.77(2H, br s), 6.78 (2H, s), 7.50 (1H, d, J=3.0Hz), 7.61 (1H, dd, J=8.1Hz), 7.81 (1H, dd, J=1.4, 6.4Hz), 8.08 (1H, dd, J=1.4Hz, 6.4Hz), 8.93 (1H, d, J=3.0Hz).

Table 33



Example #	V	X	Y	Z
316	H	Cl	H	Cl
317	H	F	F	H
318	H	F	H	F
319	Cl	Me	Me	H

EXAMPLE 316

3-chloro-4- (3,5-dichloro-phenylsulfanyl)-phenylamine (316).

A solution of potassium t-butoxide (1M in THF) (13 ml) was added via syringe to a solution of 3,5 dichlorothiophenol (2.37 g) and 3-chloro-4-fluoro-nitrobenzene (2.3 g) in THF (20 mL). The exothermic reaction was allowed to stir until it cooled to room temperature. It was poured into water. The resulting solid was collected by filtration and rinsed quickly with ether to leave the intermediate nitro compound. (3.5 g). This was dissolved in ethyl acetate at reflux. Tin (II) chloride dihydrate (2.3g) was added in portions as a solid and the reflux continued for 2 hr. After cooling, the mixture was diluted in ethyl acetate, quenched with KOH (0.5 N, 500 mL) and extracted with ethyl acetate 3 X. The organic layer was washed with water, dried over magnesium sulfate and concentrated to afford the aniline **(316)** (2.9 g) as a light tan solid useable in subsequent reactions. Mp 157-160°.

^{1}H NMR (DMSO) δ 7.36 (d, J=8.4 Hz, 1H), 7.341 (t, J=2 Hz, 1H), 6.91 (m, 2H), 6.831 (d, J=2.4 Hz, 1H), 6.602 (dd, J=8.4, 2.8 Hz, 1H), 6.01 (br s, 2H).

EXAMPLES 317 AND 318

3,4 difluorothiophenol and 3,5-difluorothiophenol were prepared by the method of D.K. Kim et al (J. Med. Chem. 40, 2363-2373 (1997) and converted by the method of example **316** to the corresponding anilines.

EXAMPLE 317

3-chloro-4- (3,5-difluoro-phenylsulfanyl)-phenylamine (317)

^{1}H NMR (DMSO) δ 7.361 (d, J=8.4 Hz, 1H), 6.983 (m, 1H), 6.84 (d, J=2.4 Hz, 1H) 6.61 (m, 3H), 6.02 (s, 2H).

EXAMPLE 318

3-chloro-4- (3,4-difluoro-phenylsulfanyl)-phenylamine (318)

^{1}H NMR (acetone) δ 7.377 (d, J=8.4 Hz, 1H), 7.258 (dt J=10.4, 8.4 Hz, 1H), 6.97 (m, 1H) 6.94 (m, 2H), 6.714 (dd, 8.4, 2.5 Hz, 1H), 5.42 (s, 2H).

EXAMPLE 319

3,5-Dichloro-4- (3,4-dimethyl-phenylsulfanyl)-phenylamine (319).

A mixture of 3,4-dimethylthiophenol (1.38g, 10mmol), 3,4,5-trichoronitrobenzene 2.49g, 11mmol) and K_2CO_3 (4.15g, 30mmol) in acetone (15ml) was

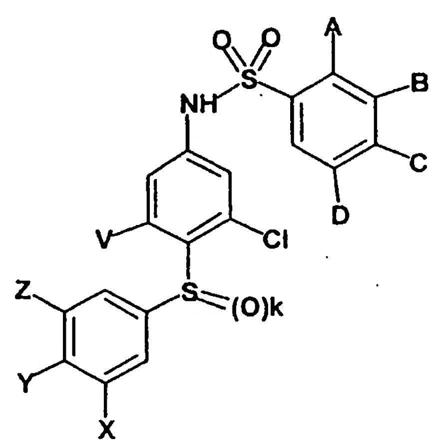
refluxed for 2 hr. After reaction mixture was concentrated, crude product was purified by column chromatography (H/A=9/1, 180g of silica gel) to afford a yellow oil. Unpurified crude 3,5-Dichloro-4- (3,4-dimethyl-phenylsulfanyl)-nitrobenzene was dissolved in CH_2Cl_2/AcOEt (5ml/20ml). To the solution was added $SnCl_2/2H_2O$(9.03g, 40mmol) and the reaction mixture was stirred at room temperature for 12 hr. 30% NaOH was added to the reaction mixture, which was extracted twice with AcOEt. Organic layer was washed by water, dried over $MgSO_4$ and concentrated to give 2.86g (96% 2 steps) of compound **319** as a white solid.

^{1}H NMR (300MHz,DMSO-d_6) δ 2.14(6H, s), 6.11(2H, br s), 6.66(1H, dd, J=1.8, 8.1Hz), 6.77(2H, s), 6.82(1H, d, J=1.8Hz), 7.02(1H, d, J=8.1Hz).

EXAMPLES 320-337

The anilines of Table 33 were sulfonylated by the method of example 3 and then oxidized to the corresponding sulfoxide by the method of example 103 or sulfone by the method of example 104 to provide the examples 320-337 illustrated in Table 34.

Table 34



EXAMPLE #	k	A	B	C	D	V	X	Y	Z	MS (M-H)
320	O	Cl	H	Cl	H	H	Cl	H	Cl	509.9
321	1	Cl	H	Cl	H	H	Cl	H	Cl	525.8
322	2	Cl	H	Cl	H	H	Cl	H	Cl	541.8
323	O	Cl	H	Cl	H	H	F	H	F	478
324	1	Cl	H	Cl	H	H	F	H	F	
325	2	Cl	H	Cl	H	H	F	H	F	509.9

326	0	Cl	H	CF_3	H	H	F	H	F	512
327	1	Cl	H	CF_3	H	H	F	H	F	461
328	2	Cl	H	CF_3	H	H	F	H	F	544
329	0	Cl	H	Cl	Me	H	F	H	F	491.9
330	1	Cl	H	Cl	Me	H	F	H	F	
331	2	Cl	H	Cl	Me	H	F	H	F	523.8
332	0	Cl	H	Cl	H	H	F	F	H	
333	1	Cl	H	Cl	H	H	F	F	H	493.9
334	2	Cl	H	Cl	H	H	F	F	H	509.9
335	0	Cl	H	CF_3	H	H	F	F	H	512
336	1	Cl	H	CF_3	H	H	F	F	H	493.9
337	2	Cl	H	CF_3	H	H	F	F	H	544
338	0	Cl	H	CF_3	H	Cl	Me	Me	H	540

EXAMPLE 324

^{1}H NMR (DMSO) δ 11.5 (br s, 1H), 8.12 (d, J=8.8 Hz, 1H), 7.88 (d, J=2 Hz, 1H), 7.748 (d, J= 8 Hz, 1H), 7.661 (dd, J=8.8, 2 Hz, 1H), 7.476 (m, 1H), 7.42 (m, 2H), 7.28 (dd, J=8.4, 2 Hz, 1H) 7.17 (br s, 1H).

EXAMPLE 330

^{1}H NMR (acetone) δ 10.1 (br s, 1H), 8.147 (s, 1H), 7.80 (d, 1H), 7.648 (s, 1H), 7.49 (m, 1H), 7.40 (m, 2H), 7.15 (d, 1H), 2.433 (s, 3H).

EXAMPLE 332

^{1}H NMR (acetone) δ 9.80 (br s, 1H), 8.162 (d, J=8.4 Hz, 1H), 7.735 (d, J=2 Hz, 1H), 7.615 (dd, J=8.4, 2.1 Hz, 1H), 7.436 (d, J= 2.2 Hz, 1H), 7.358 (dt, J=10.5, 8.4 Hz, 1H), 7.292 (ddd, 1H), 7.224 (dd, J=8.4, 2.3 Hz, 1H), 7.176 (d, J=8.4 Hz, 1H), 7.16 (m, 1H).

EXAMPLE 338

2-Chloro-N-[3,5-dichloro-4-(3,4-dimethyl-phenylsulfanyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (338)

A solution of aniline **319** (860mg, 2.68mmol) and 3-chloro-4-trifluoromethylbenzene-sulfonylchloride (658mg, 2.68mmol) in pyridine (10ml) was stirred at room temperature for 2-hr. Water was added to the reaction mixture, which was then acidified by 2N HCl. Reaction mixture was extracted twice with AcOEt. Organic layer was washed by Brine, dried over $MgSO_4$ and concentrated. Crude residue was purified by column chromatography (H/A=4/1, 80g of silica gel) to afford compound **317** (591mg, 41%) as a white solid.

^{1}H NMR (400MHz,DMSO-d_6) δ 2.11(3H,s), 2.13(3H,s), 6.78(1H,dd, J=2.1,8.3Hz), 6.81(1H,s), 7.01(1H,d, J=8.3Hz), 7.30(2H, s), 7.98(2H,dd, J=2.1,8.3Hz), 8.18(1H,s), 8.35(1H, d, J=8.3Hz), 11.6(1H, br s).

mp 156-158 °C. MS (M+H) 540.

EXAMPLE 339

3,5-Dichloro-4- (6-methyl-quinolin-3-yloxy)-phenylamine (339)

To a solution of 3-(2,6-Dichloro-4-nitro-phenoxy)-6-methyl-quinoline (309) (1.30g, 3.71mmol) and NH_4Cl (992mg, 18.55mmol) in EtOH/THF/ H_2O =12ml/12ml/3ml, was added Iron Powder (1.04g, 18.55mmol). The mixture was refluxed for 4 hr. Insoluble materials were removed by Celite filtration. The filtrate was concentrated and sat $NaHCO_3$ was added to the residue, which was then extracted twice with AcOEt. Organic layer was washed with Brine, dried over anhydrous $MgSO_4$, and concentrated to afford compound **339** (1.18g, 98%).

^{1}H NMR (300MHz,DMSO-d_6) δ 2.44 (3H, s), 5.75 (2H, br s), 6.77 (2H, s), 7.27 (1H, d, J=2.8Hz), 7.48 (1H, d, J=8.6Hz), 7.67 (1H, s), 7.89 (1H, d, J=8.6Hz), 8.74 (1H, d, J=2.8Hz).

EXAMPLE 340

2-Mercapto -4-methyl-benzothiazole (340)

The title compound was prepared using the method of example 239, starting with 2-bromo-4-methyl-phenylamine (Acros) (27.9g), *O*-ethylxanthic acid, potassium salt (Lancaster, 54g) in DMF (250 mL). The mercaptobenzothiazole **340** was obtained as an pale brown solid (27 g). Recrystalization from $CHCl_3$ gave pinkish white crystals (20g).

^{1}H NMR (DMSO-d_6) δ 7.499 (br s, 1H), 7.223 (d, J = 8 Hz, 1H), 7.198(d, J=8 Hz, 1H), 2.342 (s, 3H).

EXAMPLE 341

Compound **341** was prepared by the method of example 84.1 by coupling thiol **340** (9.3g) with 1,2,3,-trichloro-5-nitrobenzene (11.3g) in DMF using NaH as base. Trituration with ether gave **341** (12.4 g) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ 8.577 (s, 2H), 7.795 (br s, 1H), 7.736 (d, J = 8.4 Hz, 1H), 7.303 (d, J=8.4 Hz, 1H), 2.405 (s, 3H).

EXAMPLE 342

Reduction of compound **341** (12.4 g) with SnCl2 by the method of example 32 gave after trituration with methylene chloride, aniline **342** (9 g) as a solid.

^{1}H NMR (DMSO-d_6) δ 7.709 (br s, 1H), 7.699 (d, J = 8 Hz, 1H), 7.262 (d, J=8 Hz, 1H), 6.859 (s, 2H), 6.45 (s, 2H), 2.384 (s, 3H).

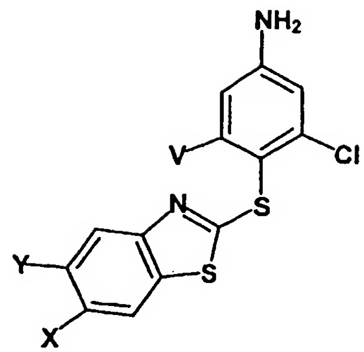
EXAMPLE 344

Compound **344** was prepared by the method of example 84.1 by coupling thiol **245** (2.01 g) with 1,2,3,-trichloro-5-nitrobenzene (2.51g) in DMF using NaH as base. Recrystalization with ether/hexane gave compound **344** (3.2 g) as a yellow solid. Mp 116-118°C.

EXAMPLE 345

Reduction of compound **344** (3.01 g) with SnCl2 by the method of example 32 gave aniline **345** (2.8 g) as a solid.

^{1}H NMR (DMSO-d_6) δ 7.772 (d, J = 8.0 Hz, 1H), 7.630 (br s, 1H), 7.155 (br d, J=8 Hz, 1H), 6.855 (s, 2H), 6.442 (s, 2H), 2.409 (s, 3H). MS (M+H) 341. Anal. Calcd.: : calc. 49.27% C, 2.95% H, 8.21% N. Found. 49.39% C, 3.16 %H, 7.98 %N



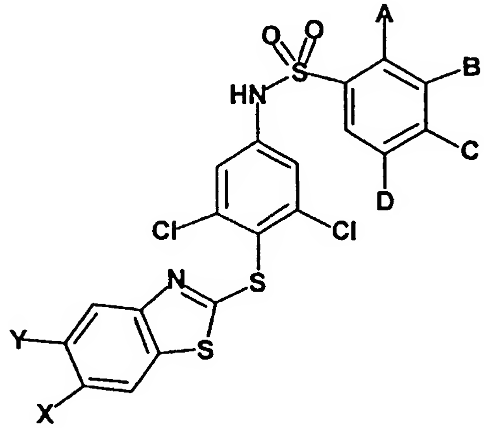
Example 342: X=Me, Y=H

Example 345: X=H, Y=Me

EXAMPLES 346-351

Sulfonylation of anilines **342** or **345** by the method of example 3 gave the sulfonamides of Table 35.

Table 35



Example #	A	B	C	D	X	Y	MS (M-H)
346	Cl	H	CF_3	H	Me	H	581
347	CF_3	H	Cl	H	Me	H	581
348	Cl	H	Cl	Me	Me	H	561
349	Cl	H	CF_3	H	H	Me	581
350	Cl	H	Cl	Me	H	Me	561
351	Cl	H	Me	H	H	Me	527

EXAMPLE 346

^{1}H NMR (DMSO-d_6) δ 11.90 (s, 1H), 8.416 (d, J = 8.0 Hz, 1H), 8.228 (br s, 1H), 8.024 (br d, J=8 Hz, 1H), 7.690 (m, 2H), 7.383 (s, 2H), 7.265 (br d, J=8 Hz, 1H), 2.379 (s, 3H). MS (M-H) 580.8.

EXAMPLE 347

^{1}H NMR(d_6-DMSO) δ 11.70-12.00 (1H, broad), 8.22 (1H, d, J = 8.6 Hz), 8.17 (1H, s), 8.08 (1H, d, J = 8.5 Hz), 7.68-7.75 (2H, m), 7.39 (2H, s), 7.28 (1H, d, J = 8.2 Hz), 2.39 (3H, s). MS (M-H) 580.8. mp 227.0 °C. Anal. Calcd.: C 43.20, H 2.07, N 4.80; found C 43.23, H 1.97, N 4.91.

EXAMPLE 348

^{1}H NMR (DMSO-d_6) δ 11.71 (br s, 1H), 8.237 (br s, 1H), 7.915 (s, 1H), 7.708 (s, 1H), 7.698 (d, J=8 Hz, 1H), 7.365 (s, 2H), 7.266 (dd, J=8, 1.6 Hz, 1H), 2.414 (s, 3H), 2.380 (s, 3H). MS (M-H) 560.8.

EXAMPLE 349

^{1}H NMR (DMSO-d_6) δ 11.94 (br s, 1H), 8.416 (d, J = 8.4 Hz, 1H), 8.231 (d, J=1.6 Hz, 1H), 8.024 (dd, J=8.4, 1.6 Hz, 1H), 7.767 (d, J=8 Hz, 1H), 7.628 (s, 1H), 7.382 (s, 2H), 7.185 (dd, J=8.4, 1.6 Hz, 1H), 2.398 (s, 3H). MS (M-H) 580.8.

EXAMPLE 350

^{1}H NMR (DMSO-d_6) δ 11.725 (br s, 1H), 8.236 (br s, 1H), 7.918 (s, 1H), 7.785 (d, J=8 Hz, 1H), 7.637 (s, 1H), 7.363 (s, 2H), 7.183 (d, J=8 Hz, 1H), 2.408 (s, 6H). MS (M-H) 560.9.

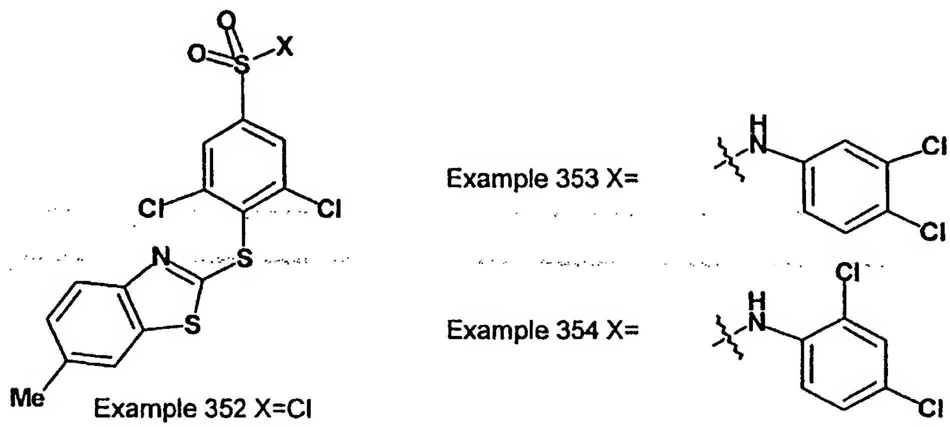
EXAMPLE 351

^{1}H NMR (d_6-DMSO) δ 11.67 (1H, s), 8.12 (1H, d, J = 8.1 Hz), 7.80 (1H, d, J = 8.2 Hz), 7.58-7.68 (2H, m), 7.46 (1H, d, J = 8.1 Hz), 7.35 (2H, s), 7.20 (1H, d, J = 8.2 Hz), 2.40 (6H, s). MS: (M-H) 526.8. mp 112.8 °C. Anal. Calcd.: 47.60%C, 2.85% H, 5.29% N; found 47.28%C, 2.98%H, 5.28%N.

EXAMPLE 352

Aniline **342** was converted according to the method of example 34 to afford the corresponding sulfonyl chloride **352** as a white solid.

^{1}H NMR ($CDCl_3$) δ 8.131 (s, 2H), 7.786 (d, J = 8.4 Hz, 1H), 7.567 (br s, 1H), 7.28 (br d, J=8 Hz, 1H), 2.482 (s, 3H).



EXAMPLE 353

Coupling of compound **352** (85 mg) with 3,4-dichloroaniline (42 mg) by the method of example 3 gave the sulfonamide **353** (76 mg) as a white solid.

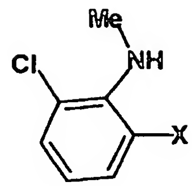
^{1}H NMR (d_6-DMSO) δ 11.01 (1H, s), 8.04 (1H, s), 7.76 (1H, s), 7.72 (1H, d, J = 8.5 Hz), 7.62 (1H, d, J = 8.7 Hz), 7.34 (1H, s), 7.29 (1H, d, J = 7.6 Hz), 7.13-7.23 (1H, m), 2.40 (3H, s). MS (M-H) 546.8. mp 181.0°C. Anal. Calcd.: calc. 43.65% C , 2.20% H, 5.09% N. found 43.10% C, 2.21% H, 4.81% N.

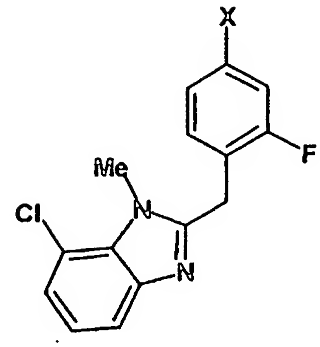
EXAMPLE 354

Coupling of compound **352** (85 mg) with 2,4-dichloroaniline (42 mg) by the method of example 3 gave after recrystalization from methanol water, the sulfonamide **354** (38 mg) as a white solid.

^{1}H NMR (d_6-DMSO) δ 10.72 (1H, s), 7.96 (2H, s), 7.79 (1H, s), 7.72-7.77 (2H, m), 7.47 (1H, dd, J = 8.7, 2.4 Hz), 7.33 (1H, d, J = 8.6 Hz), 7.31 (1H, d, J = 8.6 Hz), 2.41 (3H, s). MS (M+H) 548.9. mp 160.7°C. Anal. Calcd.: calc. 43.65% C , 2.20% H, 5.09% N. found 43.83% C, 2.19% H, 5.10% N

The following examples illustrate the synthesis of compounds **355-358**.





355 X=NO2 **357** X=NO2

356 X=NH2 **358** X=NH2

EXAMPLE 355

2,3-dichloronitrobenzene (6.15 g, 32 mmol), methylamine hydrochloride (2.38 g, 35 mmol), triethylamine (9.8 mL, 71 mmol), and DMF (16 mL) were combined in a 100 mL round-bottomed flask and heated to 90°C overnight. The reaction was then cooled to room temperature and dumped over 600 mL of ice-water. The resulting orange solid was collected by filtration and dried at the pump. Recrystallization from hot hexanes yielded 3.2 g (53%) of compound **355** as bright orange crystals.

^{1}H NMR ((d_6-DMSO) δ 7.75 (1H, dd); 7.62 (1H, dd); 6.76 (1H, t); 6.63 (1H, broad s); 2.75 (3H, t).

EXAMPLE 356

A round-bottomed flask was charged with 3.8 g (20 mmol) of compound <u>355</u>, 22.9 g (102 mmol) of tin dichloride dihydrate, and 125 mL of EtOAc. This was heated to 75°C for 3.0 hours. The reaction was cooled to room temperature, diluted with 300 mL of EtOAc and washed with 250 mL of 2N aqueous KOH solution followed by 200 mL of brine. The organics were dried over sodium sulfate and concentrated to a white amorphous solid **355** (2.9 g, 90%) that was used without further purification (turned brown upon standing in air).

^{1}H NMR (d_6-DMSO) δ 6.68 (1H, t); 6.56 (2H, m); 4.98 (2H, broad s); 3.76 (1H, broad s); 2.59 (3H, t).

EXAMPLE 357

A round-bottomed flask was charged with **356** (1.0 g, 6.4 mmol), 4-nitro-2-flourophenyl acetic acid **(148)** (1.4 g, 7.0 mmol), and 4N aqueous HCl (13 mL). This was refluxed overnight. The reaction was then cooled and basified with saturated aqueous sodium bicarbonate. The organics were extracted with methylene chloride, dried over Na_2SO_4, and concentrated to a pink solid. This was recrystallized from methylene chloride and hexanes to yield compound **357** (1.4 g, 75%) as fluffy crystals.

^{1}H NMR (400MHz) (d_6-DMSO) δ 8.16 (1H, dd); 8.08 (1H, dd); 7.62 (1H, t); 7.49 (1H, dd); 7.23 (1H, dd); 7.13 (1H, t); 4.48 (2H, s); 4.08 (3H, s).

EXAMPLE 358

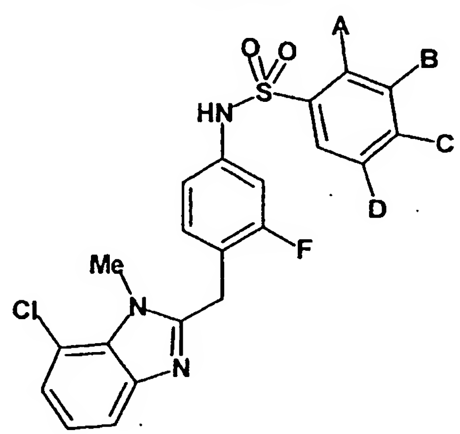
Nitro compound **357** (1.3 g, 4.0 mmol) was reduced by the method of example 356 to give the aniline **358** (1.0 g, 86%) as off-white crystals.

MS (M+H) 290.1

EXAMPLE 359-361

Aniline **358** was coupled with various sulfonyl chlorides by the method of example 192 to give the sulfonamides illustrated in Table 36

Table 36



EXAMPLE #	A	B	C	D	yield	MS (M-H)
359	Cl	H	Cl	H	36%	496
360	H	H	-COMe	H	50%	470
361	Me	H	Cl	Me	60%	

362	Cl	H	Cl	Me	496%

EXAMPLE 359

^{1}H NMR (d_6-DMSO) δ 11.01 (1H, s); 8.07 (1H, d); 7.87 (1H, d); 7.63 (1H, dd); 7.49 (1H, d); 7.22 (1H, d); 7.15 (2H, m); 6.89 (2H, m); 4.21 (2H, s); 3.99 (3H, s). MS (M-H) 496.0.

EXAMPLE 360

^{1}H NMR (d_6-DMSO) δ 10.78 (1H, s); 8.12 (2H, d); 7.94 (2H, d); 7.51 (1H, d); 7.26 (1H, d); 7.17 (2H, t); 6.97 (2H, m); 4.24 (2H, s); 4.01 (3H, s). MS (M-H) 470.1.

EXAMPLE 361

^{1}H NMR (d_6-DMSO) δ 10.75 (1H, s); 7.91 (1H, s); 7.51 (2H, m); 7.26 (1H, d); 7.16 (2H, dd); 6.88 (2H, t); 4.24 (2H, s); 4.01 (3H, s); 2.54 (3H, s); 2.34 (3H, s).

EXAMPLE 362

^{1}H NMR (d_6-DMSO) δ 10.97 (1H, s); 8.10 (1H, s); 7.83 (1H, s); 7.52 (1H, d); 7.27 (1H, d); 7.17 (2H, t); 6.94 (2H, m); 4.24 (2H, s); 4.01 (3H, s); 2.38 (3H, s).

EXAMPLE 363

This illustrates the preparation of 2,6-dichloro-benzothiazole (363).

2-Amino-6-chlorobenzothiazole (15.7g, 85mmol) in H_3PO_4 (85%)(470ml) was heated to 100 degrees and dissolved. Then clear solution was cooled and vigorously stirred by mechanical stirrer. $NaNO_2$ (17.6g, 255mmol) in water (30ml) was added slowly keeps the temperature below 0 degrees. Separately a solution of $CuSO_4/5H_2O$(85g), NaCl (107g) in water (350ml) was cooled to –5 degrees and stirred by mechanical stirrer. After Potassium Iodide Starch paper's color was disappeared Diazonium solution was keeping cold and added slowly to the copper chloride solution with vigorous stirring. The reaction Mixture was allowed to warm to room temperature. After 1-hour water (1L) and ether (1L) were added to the reaction mixture and extracted twice. Organic layer was washed by water and dried over anhydrous $MgSO_4$ and concentrated.Crude residue was purified by silica gel chromatography (H/A=4/1, 180g of silica gel) to provide title compound 363 (7.46g, 48%).

EXAMPLE 364

This illustrates the preparation of 3,5-dichloro-4- (6-chloro-benzothiazol-2-yloxy)-phenylamine.

To the solution of 4-amino-2, 6-dichloro phenol (6g, 26.5mmol) and 2,6-dichlorobenzothiazole (**363**) (6g, 29.4mmol, 1.1eq) in DMSO (25ml), was added K_2CO_3 (11g, 80mmol, 3.0eq). The mixture was stirred and heated to 160 degree. After 5.5-hr water (20ml) was added to the reaction mixture, which was neutralized with 2N HCl., and was extracted with AcOEt three times. And the organic layer was washed with Brine and was dried over anhydrous $MgSO_4$, and then concentrated. Crude residue was purified by column chromatography ($CHCl_3$/Acetone=9/1, 180g of silica gel) to afford 3,5-Dichloro-4- (6-chloro-benzothiazol-2-yloxy)-phenylamine (**364**) as a black solid (4.52g, 49%).

^{1}H NMR (300MHz,DMSO-d_6) δ 5.86(2H,br s), 6.74(2H,s), 7.48(1H,dd, J=2.1,5.7Hz), 7.70(1H,d, 8.7Hz), 8.10(1H,d, 2.1Hz).

EXAMPLE 365

This illustrates the preparation of 2-Chloro-N- [3,5-dichloro-4- (6-chloro-benzothiazol-2-yloxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**365**).

A solution of 3,5-dichloro-4- (6-chloro-benzothiazol-2-yloxy)-phenylamine (**364**) (2.0g, 5.79mmol) and 3-chloro-4-trifluoromethylbenzenesulfonylchloride (1.7g, 6.08mmol) in pyridine (10ml) was stirred at room temperature. After 3-hr water was added to the reaction mixture, which was then acidify by 2N HCl. Reaction mixture was extracted twice with AcOEt. Organic layer was washed by brine, dried over $MgSO_4$ and concentrated. Crude residue was purified by column chromatography (H/A=4/1, 80g of silica gel) to afford title compound **365** (2.11g, 65%) as a white solid. mp 82-84 °

^{1}H NMR (400MHz,DMSO-d_6) δ 7.32(2H,s), 7.46(1H,dd, J=2.2,8.7Hz), 7.67(1H,d, J=8.7Hz), 8.00(1H,d, 8.0Hz), 8.14(1H,d, J=2.2Hz), 8.20(1H,s), 8.38(1H,d, J=8.3Hz), 11.6(1H,br s). MS (M+H) 586.

EXAMPLE 366

This illustrates the preparation of 2,4-Dichloro-N-[3,5-dichloro-4-(6-chloro-benzothiazol-2-yloxy)-phenyl]benzenesulfonamide (**366**).

A solution of 3,5-dichloro-4-(6-chloro-benzothiazol-2-yloxy)-phenylamine (364) (2.0g, 5.79mmol) and 2,4-dichloro benzenesulfonylchloride (1.5g, 6.08mmol) in pyridine (10ml) was stirred at room temperature for 12-hr. Water was added to the reaction mixture, which was then acidified by 2N HCl. Reaction mixture was extracted twice with AcOEt. Organic layer was washed by Brine, dried over $MgSO_4$ and concentrated. Crude residue was purified by column chromatography (H/A=4/1, 80g of silica gel) to afford title compound (366) (1.49g, 46%) as a white solid. mp73-75 °,

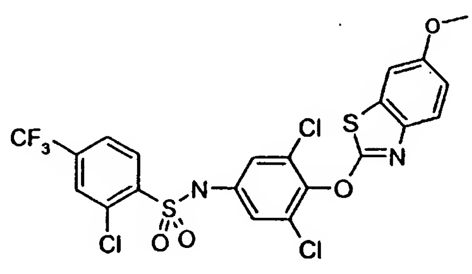
^{1}H NMR (300MHz,DMSO-d_6) δ 7.29 (2H, s), 7.46 (1H, dd, J=2.2, 8.8Hz), 7.69 (1H, d, J=8.8Hz), 7.71 (1H, dd, J=2.2, 8.4Hz), 7.95 (1H, d, J=2.2Hz), 8.14 (1H, d, J=2.2Hz), 8.18 (1H, d, J=8.4Hz), 11.5 (1H, br s). MS (M+H) 553.

EXAMPLE 367

This illustrates the preparation of 3,5-Dichloro-4-(6-methoxybenzothiazol-2-yloxy)phenylamine (367).

To a solution of 2-chloro-6-methoxybenzothiazole (prepared as described by Weinstock et.al., J.Med.Chem.30: p1166 (1987)) and 4-Amino-2,6-dichlorophenol 1.3g(available from Tokyo Chemical Industry Co., Ltd.) in DMSO(9ml), was added K_2CO_3 3.12g. The mixture was heated at 150 degree for 3hr. The reaction mixture was purified by column chromatography(silica gel, AcOEt:Hexane=1:2) to provide the aniline 367 (1.43g, 56%). mp 158-160 °

NMR(300MHz/$CDCl_3$) δ 3.84(3H, s), 3.85(2H, brs), 6.69(2H, s) 6.97(1H, dd, J=2.6Hz, J=8.9Hz), 7.18(1H, d, J=2.6Hz),7.61(1H, d, J=8.9Hz).



EXAMPLE 368

This illustrates the preparation of 2-Chloro-N-[3,5-dichloro-4-(6-methoxybenzothol-2-yloxy)-phenyl]-4-trifluoromethyl-benzenesulfonamide (368).
To a solution of 3,5-dichloro-4-(6-methoxybenzothiazol-2-yloxy)phenylamine (367) (1.40g) in pyridine (5ml), was added 2-Chloro-4-trifluorobenzenesulfonamide 1.15g. The

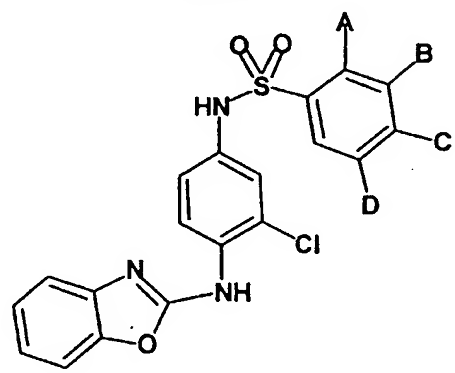
mixture was stirred at room temperature for 2hr. The reaction mixture was purified directly by column chromatography (silica gel, AcOEt:Hexane=1:3). The product was triturated by hexane to give the title compound **368** (1.97g, 82%) as a colorless powder. mp 164-165 °

NMR (300MHz/DMSO-d6) δ 3.79(3H, s), 7.00(1H, dd, J=2.9Hz, J=8.8Hz), 7.31(2H, s), 7.55(1H, d, J=8.8Hz), 7.58(1H, d, J=2.9Hz), 8.00(1H, dd, J=1.5Hz, J=8.1Hz), 8.20 (1H, d, J=1.5Hz), 8.37(1H, d, J=8.1Hz), 11.59(1H, brs). MS (M+H) 583.

EXAMPLES 369-370

The examples illustrated in Table 37, were prepared from aniline **75** and the corresponding sulfonyl chlorides by the method of procedure 3. The compounds were purified by chromatography on silica gel.

Table 37



Example #	A	B	C	D	MS (M-H)
369	Cl	H	Cl	H	466
370	H	Cl	Cl	H	466
371	Me	H	Cl	Me	460
372	Cl	H	Cl	Me	480

EXAMPLE 369

^{1}H NMR (d6-acetone) δ 9.54 (br s, 1H), 8.82 (br s, 1H), 8.446 (d, J=8.8 Hz, 1H), 8.129 (d, J=8.4 Hz, 1H), 7.763 (d, J=2 Hz, 1H), 7.602 (dd, J=8.4, 2 Hz, 1H), 7.428 (m, 2H), 7.327 (dd, J=9.2, 2.4 Hz, 1H), 7.252 (td, J=7.6, 1.2 Hz, 1H), 7.17 (td, J=8, 1.2 Hz, 1H). MS (M-H) 466.0.

EXAMPLE 370

^{1}H NMR (d6-DMSO) δ 10.643 (br s, 1H), 9.954 (br s, 1H), 7.983 (d, J=2 Hz, 1H), 7.934 (br d, J=8 Hz, 1H), 7.885 (d, J=8.4 Hz, 1H), 7.717 (dd, J=8.4, 2.4 Hz, 1H), 7.454 (d, J=8 Hz, 1H), 7.360 (br d, J=7.6 Hz, 1H), 7.226 (d, J=2 Hz, 1H), 7.194 (t, J=8 Hz, 1H), 7.142 (dd, J=8.8, 2 Hz, 1H), 7.106 (t, J=8 Hz, 1H). MS (M-H) 466.0.

EXAMPLE 371

^{1}H NMR (d6-acetone) δ 9.31 (br s, 1H), 8.80 (br s, 1H), 8.403 (d, J=8 Hz, 1H), 7.928 (s, 1H), 7.45-7.35 (m, 4H), 7.3-7.2 (m, 2H), 7.164 (br t, J=8 Hz, 1H), 2.64 (s, 3H), 2.387 (s, 3H). MS (M-H) 460.0.

EXAMPLE 372

^{1}H NMR (d6-acetone) δ 9.48 (br s, 1H), 8.82 (br s, 1H), 8.064 (s, 1H), 7.707 (s, 1H), 7.45-7.40 (m, 4H), 7.335 (dd, J=8.8, 2HZ, 1H), 7.252 (td, J=7.6, 1.2 Hz, 1H), 7.19 (td, J=8, 1.2 Hz, 1H) 2.425 (s, 3H). MS (M-H) 479.9.

EXAMPLE 373

Using methods similar to Lehmann, *et al., ibid.*, selected compounds exhibited the following IC_{50} values in a PPARγ ligand binding assay utilizing [^{3}H]-BRL 49653 as the radioligand. IC_{50} values are defined as the concentration of test compounds required to reduce by 50% the specific binding of [^{3}H]-BRL 49653 and are represented by (+) <30 μM; (++) < 10 μM; (+++) < 1 μM.

TABLE 38

Compound	IC_{50}(μM)
4.1	+++
16.1	+++
27.3	++
27.5	++
49.1	+++
50.1	+++
72.2	++

72.3	+++
72.4	++
73.4	+++
73.5	+++
73.6	+++
73.7	+++
73.8	+++
73.9	+++
79.5	+++
86	+++
87.3	+++
95	+++
97	+++
108.4	+++
158	+++
160	+++
178	+++
179	+++
219	+++
233	+++
290	+++
292	+++
349	+++
364	++
365	++
368	+++

EXAMPLE 374

Selected compounds were administered to KK-Ay mice as a 0.018% (30 mg/kg) dietary admixture in powdered diet and evaluated for anti-diabetic efficacy as described (T. Shibata, K. Matsui, K. Nagao, H. Shinkai, F. Yonemori and K. Wakitani 1999; *European Journal of Pharmacology* 364:211-219). The change in serum glucose levels compared to untreated control animals is exemplified in Table 39.

TABLE 39

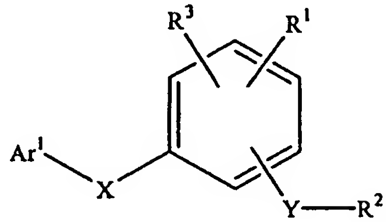
Example #	KKAy Glucose
87.3	++
178	++
179	++
219	+
233	-
364	+
365	++

(-) <10%; (+) 10% to 20%; (++) glucose lowering >20%.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein

Ar^1 is a substituted or unsubstituted aryl;

X is a divalent linkage selected from the group consisting of $(C_1$-$C_6)$alkylene, $(C_1$-$C_6)$alkylenoxy, $(C_1$-$C_6)$alkylenamino, $(C_1$-$C_6)$alkylene-$S(O)_k$-, -O-, -C(O)-, -$N(R^{11})$-, -$N(R^{11})C(O)$-, -$S(O)_k$- and a single bond,

wherein

R^{11} is a member selected from the group consisting of hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$heteroalkyl and aryl$(C_1$-$C_4)$alkyl; and the subscript k is an integer of from 0 to 2;

Y is a divalent linkage selected from the group consisting of $(C_1$-$C_6)$alkylene, -O-, -C(O)-, -$N(R^{12})$-$S(O)_m$-,-$N(R^{12})$-$S(O)_m$-$N(R^{13})$-, -$N(R^{12})C(O)$-, -$S(O)_n$- and a single bond,

wherein

R^{12} and R^{13} are members independently selected from the group consisting of hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$heteroalkyl and aryl$(C_1$-$C_4)$alkyl; and the subscripts m and n are independently integers of from 0 to 2;

R^1 is a member selected from the group consisting of hydrogen, $(C_2$-$C_8)$heteroalkyl, aryl, aryl$(C_1$-$C_4)$alkyl, halogen, cyano, nitro, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, -$C(O)R^{14}$, -CO_2R^{14}, -$C(O)NR^{15}R^{16}$, -$S(O)_p$-R^{14}, -$S(O)_q$-$NR^{15}R^{16}$, -O-C(O)-OR^{17}, -O-C(O)-R^{17}, -O-C(O)-$NR^{15}R^{16}$, -$N(R^{14})$-C(O)-$NR^{15}R^{16}$, -$N(R^{14})$-C(O)-R^{17} and –$N(R^{14})$-C(O)-OR^{17};

wherein

R^{14} is a member selected from the group consisting of hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$heteroalkyl, aryl and aryl$(C_1$-$C_4)$alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl, aryl, and aryl$(C_1\text{-}C_4)$alkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl, aryl and aryl$(C_1\text{-}C_4)$alkyl;

the subscript p is an integer of from 0 to 3; and

the subscript q is an integer of from 1 to 2; and

R^2 is a substituted or unsubstituted aryl; and

R^3 is a member selected from the group consisting of halogen, cyano, nitro and $(C_1\text{-}C_8)$alkoxy.

2. A compound of claim 1, wherein X is a divalent linkage selected from the group consisting of substituted or unsubstituted $(C_1\text{-}C_6)$alkylene, -O-, -C(O)-, -N(R^{11})- and –S(O)$_k$-.

3. A compound of claim 1, wherein X is a divalent linkage selected from the group consisting of –CH_2-, -CH(CH_3)-, -CH(CH_2CH_3)-, -CH(isopropyl)-, -CH(CN)-, -O-, -C(O)-, -N(R^{11})- and –S(O)$_k$-.

4. A compound of claim 1, wherein Y is -N(R^{12})-S(O)$_2$-, wherein R^{12} is a member selected from the group consisting of hydrogen and $(C_1\text{-}C_8)$alkyl.

5. A compound of claim 1, wherein X is a divalent linkage selected from the group consisting of –CH_2-, -CH(CH_3)-, -O-, -C(O)-, -N(R^{11})- and –S-; and Y is -N(R^{12})-S(O)$_2$-, wherein R^{12} is a member selected from the group consisting of hydrogen and $(C_1\text{-}C_8)$alkyl.

6. A compound of claim 1, wherein R^2 is a substituted or unsubstituted aryl selected from the group consisting of phenyl, pyridyl, naphthyl and pyridazinyl.

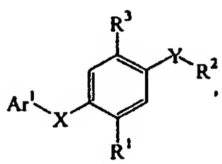
7. A compound of claim 1, wherein X is a divalent linkage selected from the group consisting of –CH_2-, -CH(CH_3)-, -O-, -C(O)-, -N(R^{11})- and –S-; Y is -N(R^{12})-S(O)$_2$-, wherein R^{12} is a member selected from the group consisting of hydrogen

and $(C_1\text{-}C_8)$alkyl; and R^2 is a substituted or unsubstituted aryl selected from the group consisting of phenyl, pyridyl, naphthyl and pyridazinyl.

8. A compound of claim 1, wherein Ar^1 is a substituted or unsubstituted aryl selected from the group consisting of pyridyl, phenyl, naphthyl, quinolinyl, isoquinolinyl, benzoxazolyl, benzothiazolyl, and benzimidazolyl.

9. A compound of claim 8, wherein Ar^1 is a substituted or unsubstituted phenyl group.

10. A compound of claim 9, represented by a formula selected from the group consisting of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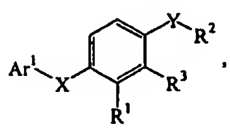
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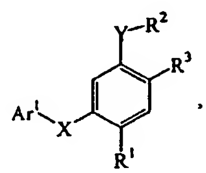
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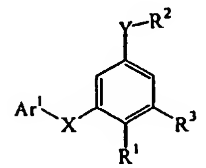
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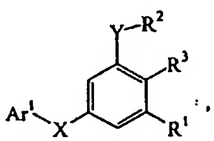
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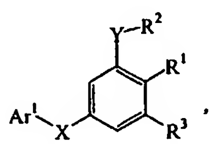
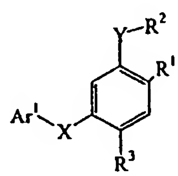
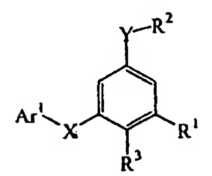
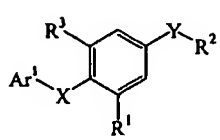
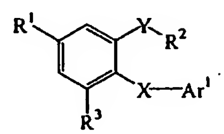

(If)


(Ig)


(Ih)

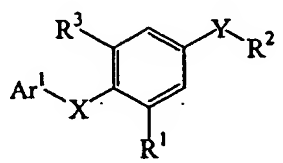

(Ii)

and


(Ij)

11. A compound of claim 10, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of hydrogen, halogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl, $(C_1\text{-}C_8)$alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O$(C_1\text{-}C_8)$alkyl, -C(O)-$(C_1\text{-}C_8)$alkyl, -CN, -CF_3, $(C_1\text{-}C_8)$alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

12. A compound of claim 9, represented by a formula selected from the group consisting of



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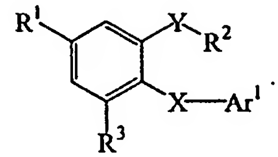


(Ii) (Ij) .

13. A compound of claim 12, wherein

X is a divalent linkage selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, -O-, -C(O)-, $-N(R^{11})-$ and –S-;

wherein

R^{11} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

Y is a divalent linkage selected from the group consisting of $-N(R^{12})-S(O)_2-$,

wherein

R^{12} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$, $-S(O)_q-NR^{15}R^{16}$, $-O-C(O)-R^{17}$, and $-N(R^{14})-C(O)-R^{17}$;

wherein

R^{14} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R^2 is a substituted or unsubstituted phenyl; and

R^3 is a member selected from the group consisting of halogen and (C_1-C_8)alkoxy.

14. A compound of claim 13, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

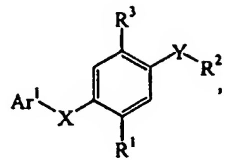
15. A compound of claim 14, wherein Ar^1 is a phenyl group having from 1 to 3 substituents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_6)alkyl, -CF_3, (C_1-C_8)alkyl and -NO_2; R^1 is a member selected from the group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

16. A compound of claim 15, wherein R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, -OCF_3, and -CF_3.

17. A compound of claim 15, wherein, R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, -OCF_3, and -CF_3.

18. A compound of claim 8, wherein Ar^1 is a substituted or unsubstituted pyridyl group.

19. A compound of claim 18, represented by a formula selected from the group consisting of



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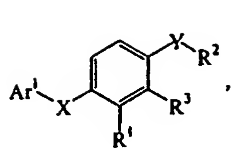
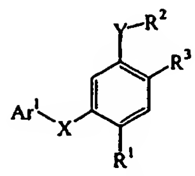
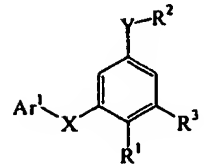


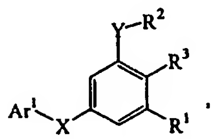
(Ib)



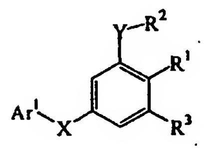
(Ic)



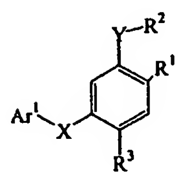
(Id)



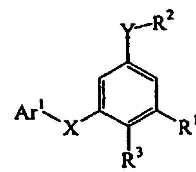
(Ie)



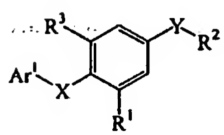
(If)



(Ig)

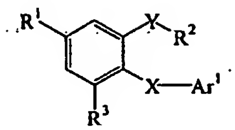


(Ih)



(Ii)

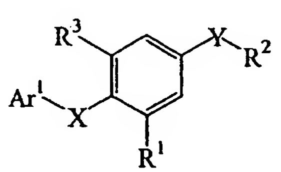
and



(Ij)

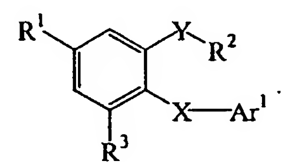
20. A compound of claim 19, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substituents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

21. A compound of claim 19, represented by a formula selected from the group consisting of



(Ii)

and



(Ij)

22. A compound of claim 21, wherein

X is a divalent linkage selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, $-O-$, $-C(O)-$, $-N(R^{11})-$ and $-S-$;

wherein

R^{11} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

Y is a divalent linkage selected from the group consisting of $-N(R^{12})-S(O)_2-$,

wherein

R^{12} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$, $-S(O)_q-NR^{15}R^{16}$, $-O-C(O)-R^{17}$, and $-N(R^{14})-C(O)-R^{17}$;

wherein

R^{14} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R^2 is a substituted or unsubstituted phenyl; and

R^3 is a member selected from the group consisting of halogen and (C_1-C_8)alkoxy.

23. A compound of claim 22, wherein X is $-O-$, $-NH-$ or $-S-$; Y is $-NH-SO_2-$; R^1 is a member selected from the group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, $-OH$, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, $-CN$, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

24. A compound of claim 23, wherein Ar^1 is a pyridyl group having from 1 to 3 substituents selected from the group consisting of halogen, $-OCF_3$, $-OH$, $-O(C_1-C_6)$alkyl, $-CF_3$, (C_1-C_8)alkyl and $-NO_2$; R^1 is a member selected from the group

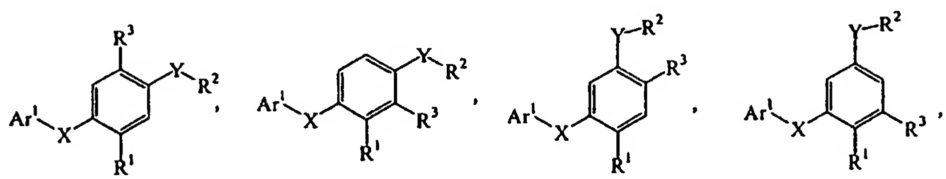
consisting of halogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl and $(C_1\text{-}C_8)$alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O$(C_1\text{-}C_8)$alkyl, -C(O)-$(C_1\text{-}C_8)$alkyl, -CN, -CF_3, $(C_1\text{-}C_8)$alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

25. A compound of claim **24**, wherein R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, -OCF_3, and -CF_3.

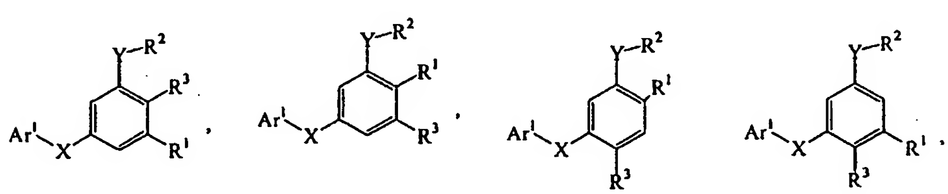
26. A compound of claim **25**, wherein, R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, -OCF_3, and -CF_3.

27. A compound of claim **8**, wherein Ar^1 is a substituted or unsubstituted naphthyl group.

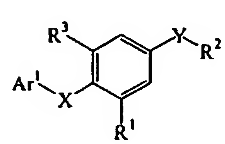
28. A compound of claim **27**, represented by a formula selected from the group consisting of



(Ia) (Ib) (Ic) (Id)



(Ie) (If) (Ig) (Ih)



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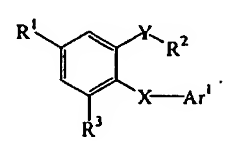
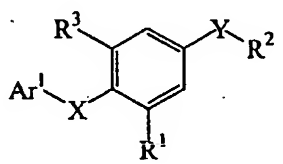


(Ii) (Ij)

29. A compound of claim **28**, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-

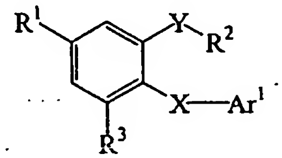
C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

30. A compound of claim 28, represented by a formula selected from the group consisting of



(Ii)

and



(Ij)

31. A compound of claim 30, wherein

X is a divalent linkage selected from the group consisting of –CH_2-, -CH(CH_3)-, -O-, -C(O)-, -N(R^{11})- and –S-;

wherein

R^{11} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

Y is a divalent linkage selected from the group consisting of -N(R^{12})-$S(O)_2$-,

wherein

R^{12} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14}, -$S(O)_q$-$NR^{15}R^{16}$, -O-C(O)-R^{17}, and -N(R^{14})-C(O)-R^{17};

wherein

R^{14} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of hydrogen, $(C_1$-$C_8)$alkyl and $(C_2$-$C_8)$heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R^2 is a substituted or unsubstituted phenyl; and

R^3 is a member selected from the group consisting of halogen and $(C_1$-$C_8)$alkoxy.

32. A compound of claim 31, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of halogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$heteroalkyl, $(C_1$-$C_8)$alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O$(C_1$-$C_8)$alkyl, -C(O)-$(C_1$-$C_8)$alkyl, -CN, -CF_3, $(C_1$-$C_8)$alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

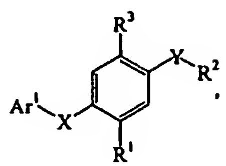
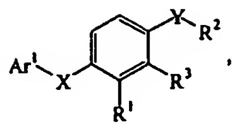
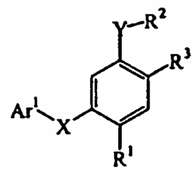
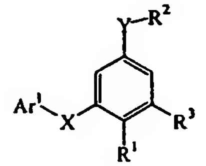
33. A compound of claim 32, wherein Ar^1 is a naphthyl group having from 0 to 3 substituents selected from the group consisting of halogen, -OCF_3, -OH, -O$(C_1$-$C_6)$alkyl, -CF_3, $(C_1$-$C_8)$alkyl and -NO_2; R^1 is a member selected from the group consisting of halogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$heteroalkyl and $(C_1$-$C_8)$alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O$(C_1$-$C_8)$alkyl, -C(O)-$(C_1$-$C_8)$alkyl, -CN, -CF_3, $(C_1$-$C_8)$alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

34. A compound of claim 33, wherein R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, -OCF_3, and -CF_3.

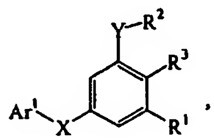
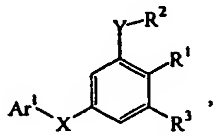
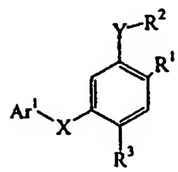
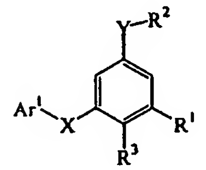
35. A compound of claim 34, wherein, R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, -OCF_3, and -CF_3.

36 A compound of claim 8, wherein Ar^1 is a substituted or unsubstituted benzothiazolyl group.

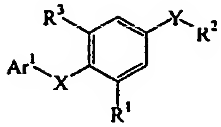
37. A compound of claim 36, represented by a formula selected from the group consisting of

 ,
 ,
 ,
 ,

(Ia) (Ib) (Ic) (Id)

 ,
 ,

 ,

(Ie) (If) (Ig) (Ih)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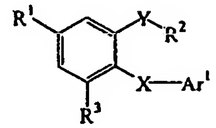
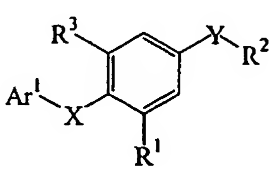


(Ii) (Ij) .

38. A compound of claim 37, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

39. A compound of claim 37, represented by a formula selected from the group consisting of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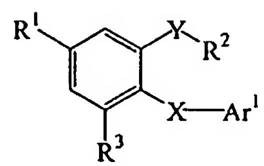


(Ii) (Ij) .

40. A compound of claim 39, wherein

X is a divalent linkage selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, -O-, -C(O)-, $-N(R^{11})-$ and –S-;

wherein

R^{11} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

Y is a divalent linkage selected from the group consisting of $-N(R^{12})-S(O)_2-$,

wherein

R^{12} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$, $-S(O)_q-NR^{15}R^{16}$, $-O-C(O)-R^{17}$, and $-N(R^{14})-C(O)-R^{17}$;

wherein

R^{14} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R^2 is a substituted or unsubstituted phenyl; and

R^3 is a member selected from the group consisting of halogen and (C_1-C_8)alkoxy.

41. A compound of claim 40, wherein X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from the group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

42. A compound of claim 41, wherein Ar^1 is a benzothiazolyl group having from 0 to 3 substituents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_6)$alkyl, $-CF_3$, (C_1-C_8)alkyl and $-NO_2$; R^1 is a member selected from the

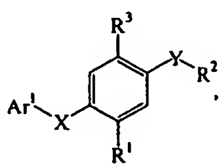
group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

43. A compound of claim **42**, wherein R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, and $-CF_3$.

44. A compound of claim **43**, wherein, R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, and $-CF_3$.

45. A compound of claim **8**, wherein Ar^1 is a substituted or unsubstituted benzoxazolyl group.

46. A compound of claim **45**, represented by a formula selected from the group consisting of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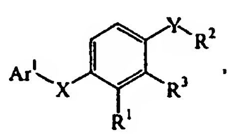
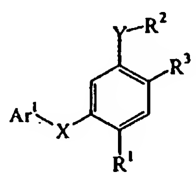
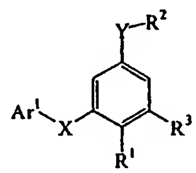

(Ib)


(Ic)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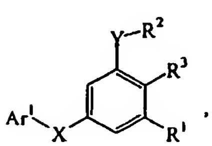
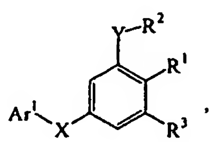

(Ie)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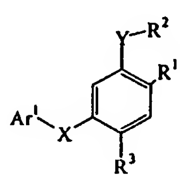
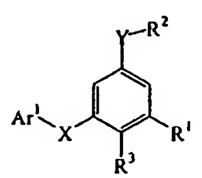
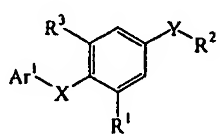
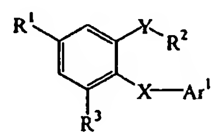

(Ig)


(Ih)

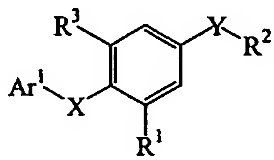

(Ii)

and


(Ij)

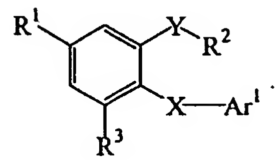
47. A compound of claim 46, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

48. A compound of claim 46, represented by a formula selected from the group consisting of



(Ii)

and



(Ij)

49. A compound of claim 48, wherein

X is a divalent linkage selected from the group consisting of –CH_2-, -CH(CH_3)-, -O-, -C(O)-, -N(R^{11})- and –S-;

wherein

R^{11} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

Y is a divalent linkage selected from the group consisting of -N(R^{12})-$S(O)_2$-,

wherein

R^{12} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14}, -$S(O)_q$-$NR^{15}R^{16}$, -O-C(O)-R^{17}, and -N(R^{14})-C(O)-R^{17};

wherein

R^{14} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together

with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R^2 is a substituted or unsubstituted phenyl; and

R^3 is a member selected from the group consisting of halogen and (C_1-C_8)alkoxy.

50. A compound of claim 49, wherein X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from the group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

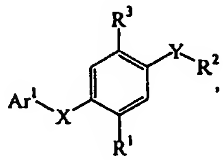
51. A compound of claim 50, wherein Ar^1 is a benzoxazolyl group having from 0 to 3 substituents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_6)$alkyl, $-CF_3$, (C_1-C_8)alkyl and $-NO_2$; R^1 is a member selected from the group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

52. A compound of claim 51, wherein R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, and $-CF_3$.

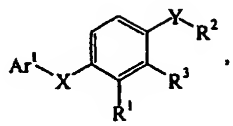
53. A compound of claim 52, wherein, R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, and $-CF_3$.

54. A compound of claim 8, wherein Ar^1 is a substituted or unsubstituted benzimidazolyl group.

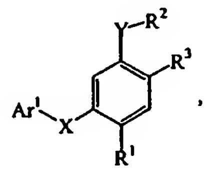
55. A compound of claim 54, represented by a formula selected from the group consisting of



(Ia)



(Ib)



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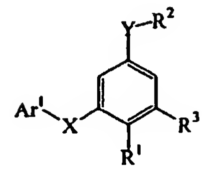

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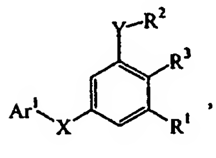

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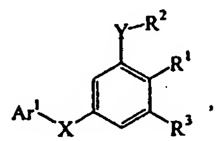

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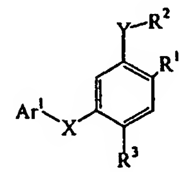

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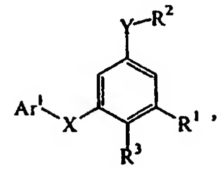
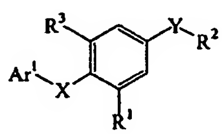
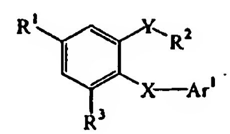


(Ih)



(Ii)

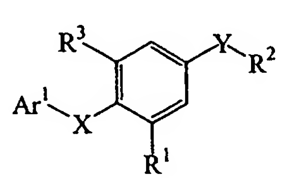
and



(Ij)

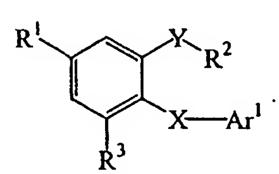
56. A compound of claim 55, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

57. A compound of claim 55, represented by a formula selected from the group consisting of



(Ii)

and



(Ij)

58. A compound of claim 57, wherein

X is a divalent linkage selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, -O-, -C(O)-, $-N(R^{11})-$ and –S-;

wherein

R^{11} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

Y is a divalent linkage selected from the group consisting of $-N(R^{12})-S(O)_2-$,

wherein

R^{12} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$, $-S(O)_q-NR^{15}R^{16}$, $-O-C(O)-R^{17}$, and $-N(R^{14})-C(O)-R^{17}$;

wherein

R^{14} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R^2 is a substituted or unsubstituted phenyl; and

R^3 is a member selected from the group consisting of halogen and (C_1-C_8)alkoxy.

59. A compound of claim 58, wherein X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from the group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

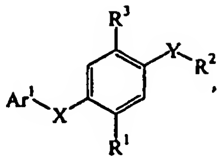
60. A compound of claim 59, wherein Ar^1 is a benzimidazolyl group having from 0 to 3 substituents selected from the group consisting of halogen, $-OCF_3$, $-OH$, $-O(C_1-C_6)$alkyl, $-CF_3$, (C_1-C_8)alkyl and $-NO_2$; R^1 is a member selected from the group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl and (C_1-C_8)alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, $-OH$, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, $-CN$, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

61. A compound of claim 60, wherein R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, and $-CF_3$.

62. A compound of claim 61, wherein, R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, and $-CF_3$.

63. A compound of claim 8, wherein Ar^1 is a substituted or unsubstituted quinolinyl or isoquinolinyl group.

64. A compound of claim 63, represented by a formula selected from the group consisting of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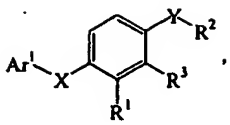
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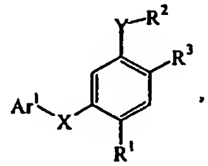
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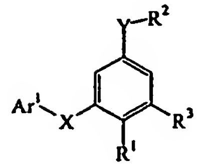
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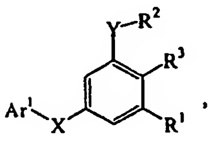
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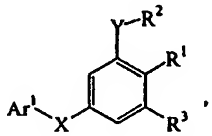
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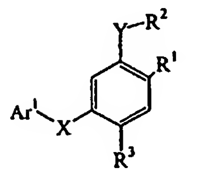
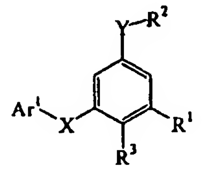

(Ig)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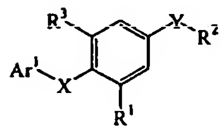
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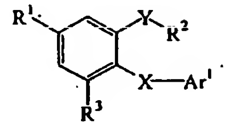
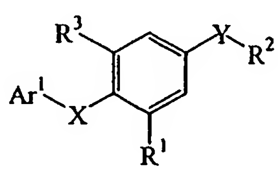
and

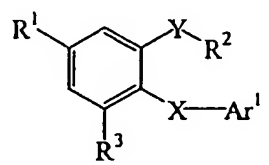

(Ij)

65. A compound of claim 64, wherein X is –O-, -NH- or –S-; Y is -NH-SO_2-; R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, -C(O)R^{14}, -CO_2R^{14}, -C(O)$NR^{15}R^{16}$, -$S(O)_p$-R^{14} and -$S(O)_q$-$NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, -OCF_3, -OH, -O(C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkyl, -CN, -CF_3, (C_1-C_8)alkyl and -NH_2; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

66. A compound of claim 64, represented by a formula selected from the group consisting of


(Ii)

and


(Ij)

67. A compound of claim 66, wherein

X is a divalent linkage selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, -O-, -C(O)-, $-N(R^{11})-$ and –S-;

wherein

R^{11} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

Y is a divalent linkage selected from the group consisting of $-N(R^{12})-S(O)_2-$,

wherein

R^{12} is a member selected from the group consisting of hydrogen and (C_1-C_8)alkyl;

R^1 is a member selected from the group consisting of hydrogen, halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$, $-S(O)_q-NR^{15}R^{16}$, $-O-C(O)-R^{17}$, and $-N(R^{14})-C(O)-R^{17}$;

wherein

R^{14} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, aryl and aryl(C_1-C_4)alkyl;

R^{15} and R^{16} are members independently selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl, or taken together with the nitrogen to which each is attached form a 5-, 6- or 7-membered ring;

R^{17} is a member selected from the group consisting of hydrogen, (C_1-C_8)alkyl and (C_2-C_8)heteroalkyl;

the subscript p is an integer of from 0 to 2; and

the subscript q is 2; and

R^2 is a substituted or unsubstituted phenyl; and

R^3 is a member selected from the group consisting of halogen and (C_1-C_8)alkoxy.

68. A compound of claim **67**, wherein X is –O-, -NH- or –S-; Y is $-NH-SO_2-$; R^1 is a member selected from the group consisting of halogen, (C_1-C_8)alkyl, (C_2-C_8)heteroalkyl, (C_1-C_8)alkoxy, $-C(O)R^{14}$, $-CO_2R^{14}$, $-C(O)NR^{15}R^{16}$, $-S(O)_p-R^{14}$ and $-S(O)_q-NR^{15}R^{16}$; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_8)$alkyl, $-C(O)-(C_1-C_8)$alkyl, -CN, $-CF_3$, (C_1-C_8)alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

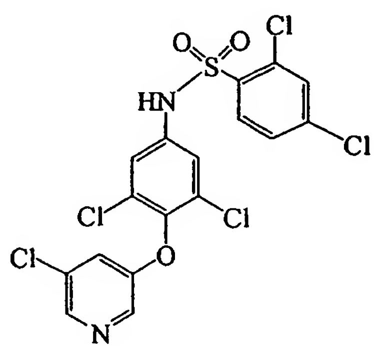
69. A compound of claim **68**, wherein Ar^1 is a benzimidazolyl group having from 0 to 3 substituents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1-C_6)$alkyl, $-CF_3$, (C_1-C_8)alkyl and $-NO_2$; R^1 is a member selected from the

group consisting of halogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$heteroalkyl and $(C_1\text{-}C_8)$alkoxy; R^2 is a phenyl group having from 0 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, -OH, $-O(C_1\text{-}C_8)$alkyl, $-C(O)\text{-}(C_1\text{-}C_8)$alkyl, -CN, $-CF_3$, $(C_1\text{-}C_8)$alkyl and $-NH_2$; and R^3 is selected from the group consisting of halogen, methoxy and trifluoromethoxy.

70. A compound of claim 69, wherein R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, and $-CF_3$.

71. A compound of claim 69, wherein, R^1 and R^3 are each independently a halogen, and R^2 is a phenyl group having from 1 to 3 substitutents selected from the group consisting of halogen, $-OCF_3$, and $-CF_3$.

72. A compound of claim 1, selected from the group consisting of



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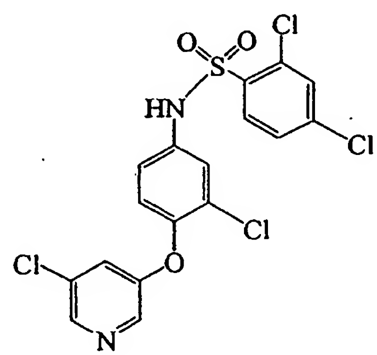
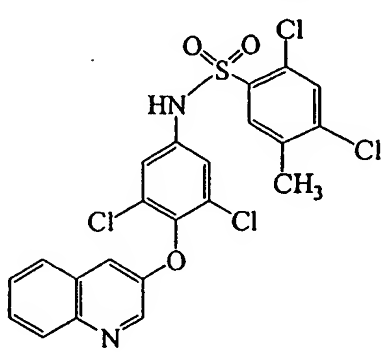


73. A compound of claim 1, selected from the group consisting of



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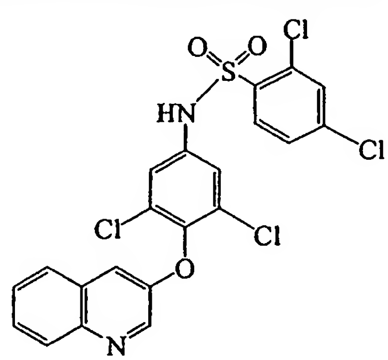
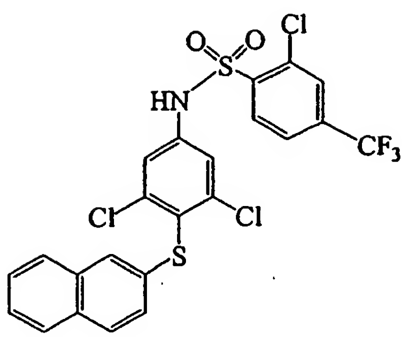


74. A compound of claim 1, selected from the group consisting of



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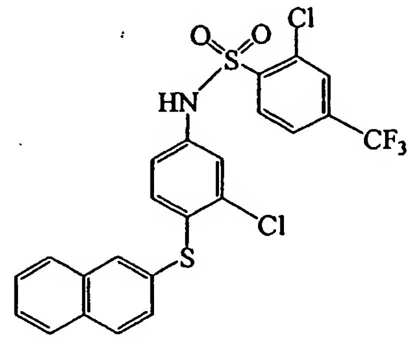
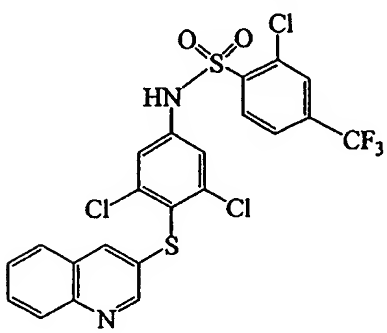
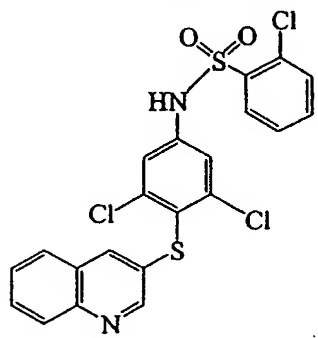


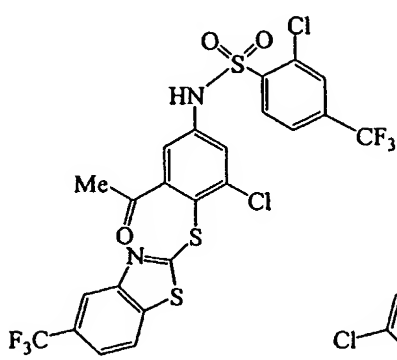
75. A compound of claim 1, selected from the group consisting of:



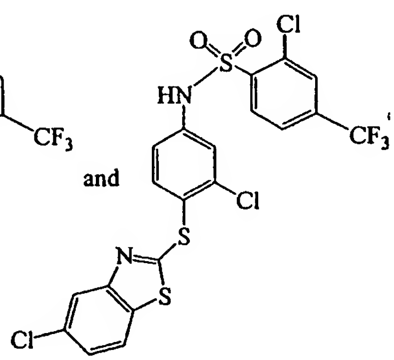
and



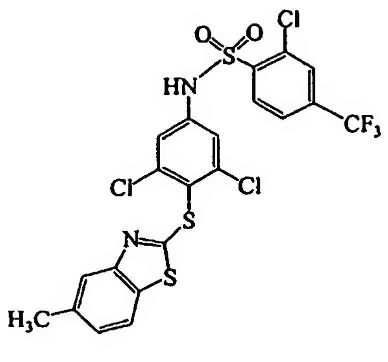
76. A compound of claim 1, selected from the group consisting of:



and



77. A compound of claim 1, selected from the group consisting of:



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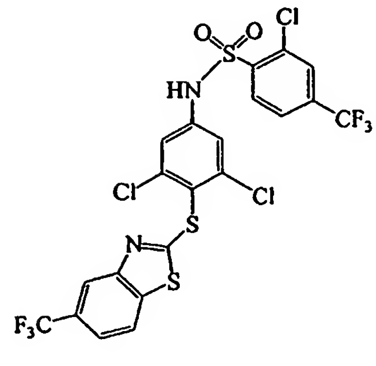

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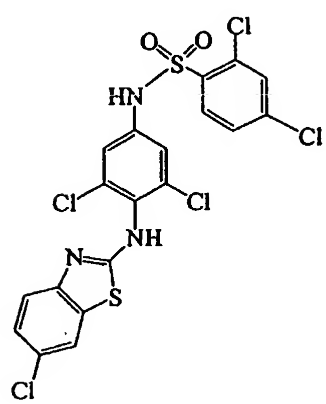
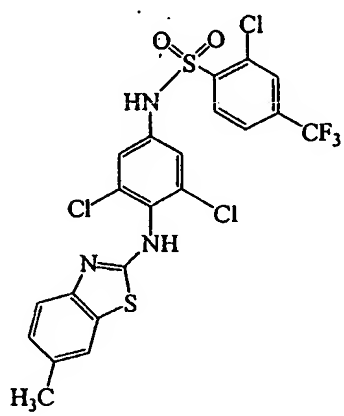
78. A compound of claim 1, selected from the group consisting of:



and



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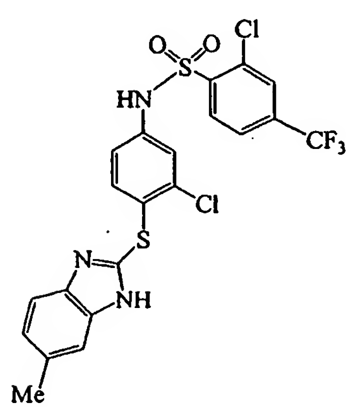
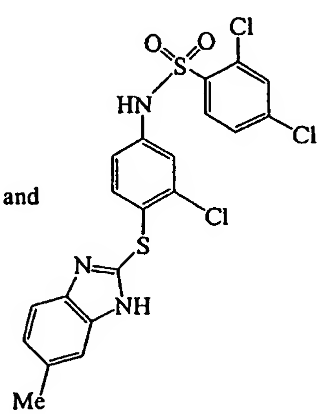
79. A compound of claim 1, selected from the group consisting of:



and



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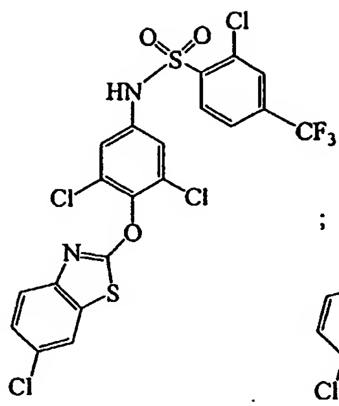
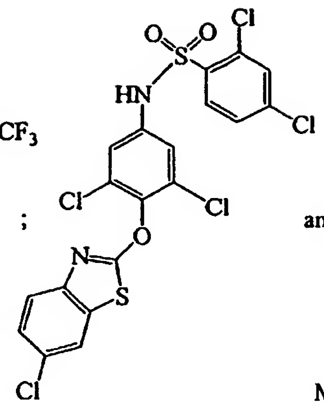
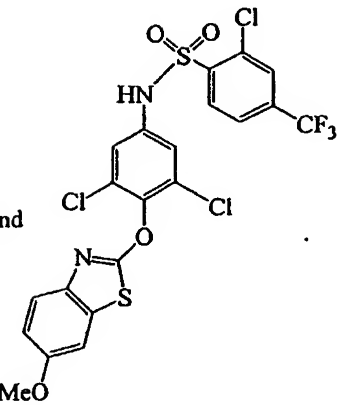
80. A compound of claim 1, selected from the group consisting of:


;

and

.

81. A composition comprising a pharmaceutically acceptable excipient and a compound of any of claims 1-80.

82. A method for modulating conditions associated with metabolic or inflammatory disorders in a host, said method comprising administering to said host an efficacious amount of a compound of any of claims 1-80.

83. A method in accordance with claim 82, wherein said host is a mammal selected from the group consisting of humans, dogs, monkeys, mice, rats, horses and cats.

84. A method in accordance with claim 82, wherein said administering is oral.

85. A method in accordance with claim 82, wherein said administering is topical.

86. A method in accordance with claim 82, wherein said administering is prophylactic to prevent the onset of a PPARγ-mediated condition.

87. A method in accordance with claim 82, wherein said disorders are selected from the group consisting of NIDDM, obesity, hypercholesterolemia and other lipid-mediated diseases, and inflammatory conditions.

88. A method in accordance with claim 82, wherein said administering is parenteral.

89. A method in accordance with claim 82, wherein said metabolic disorders are mediated by PPARγ.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/18178

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/65 C07D215/36 C07D215/20 C07D277/74 C07D211/82 C07D277/68 C07D235/28 C07C311/21 A61K31/18 A61K31/44 A61K31/415 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 855 391 A (SNOW BRAND MILK PROD CO LTD) 29 July 1998 (1998-07-29) see compounds pages 90,95,101	1-3,8, 63,64,66
X	EP 0 749 751 A (TAKEDA CHEMICAL INDUSTRIES LTD) 27 December 1996 (1996-12-27) compound (III), page 3	1,8,18, 19,81
X	EP 0 261 539 A (BAYER AG) 30 March 1988 (1988-03-30) examples 60,61	1-3, 63-67,81
X	EP 0 069 585 A (EASTMAN KODAK CO) 12 January 1983 (1983-01-12) compounds pages 18,43,47; examples 20,134	1-13,81

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2000	13/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 01326 A (WELLCOME FOUND ;ARROWSMITH RICHARD JAMES (GB); DANN JOHN GORDON (G) 12 January 1995 (1995-01-12) example 24	1-3,81
X	examples 38,41	1-3,8,81
X	examples 20,40	1-13,81
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A	WO 99 06378 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US)) 11 February 1999 (1999-02-11) compounds page 26, lines 18,20,22,24,26,29; page 27, lines 1,4,7,9,12,14,16,18,20,22,24,26,28,30, page 28, lines 1,2, etc	1-3,81
A	WO 99 10320 A (TULARIK INC) 4 March 1999 (1999-03-04) abstract; claims	1-89
A	WO 97 31907 A (GLAXO GROUP LTD ;WILLSON TIMOTHY MARK (US); MOOK ROBERT ANTHONY JR) 4 September 1997 (1997-09-04) abstract; claims	1-89
A,P	WO 99 38845 A (TULARIK INC) 5 August 1999 (1999-08-05) the whole document	1-89
A	LEHMANN J M ET AL: "PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS ALPHA AND GAMMA ARE ACTIVATED BY INDOMETHACIN AND OTHER NON-STEROIDAL ANTI-INFLAMMATORYDRUGS" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 272, no. 6, 7 February 1997 (1997-02-07), pages 3406-3410, XP002923816 ISSN: 0021-9258 the whole document	1-89

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WILLSON T M ET AL: "THE STRUCTURE-ACTIVITY RELATIONSHIP BETWEEN PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AGONISM AND THE ANTIHYPERGLYCEMIC ACTIVITY OF THIAZOLIDINEDIONES" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 39, no. 3, 2 February 1996 (1996-02-02), pages 665-668, XP000613613 ISSN: 0022-2623 the whole document ---	1-89
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X	DATABASE CHEMABS 'Online! CAS; BURMISTROV K.S. ET AL.: retrieved from STN Database accession no. 122:132338 XP002148690 RN 134284-40-5 & ZH. ORG. KHIM., vol. 30, no. 5, 1994, pages 744-747, ---	1-14
X	DATABASE CHEMABS 'Online! CAS; SEBE, ION ET AL.: retrieved from STN Database accession no. 117:214517 XP002148691 rnS 144206-02-0, 144232-65-5 & REV. CHIM., vol. 43, no. 5-6, 1992, pages 222-225, ---	1-7
X	DATABASE CHEMABS 'Online! CAS; BURMISTROV K.S. ET AL.: retrieved from STN Database accession no. 115:8165 XP002148692 RNS 98187-76-9, 134284-40-5 & ZH. ORG. KHIM., vol. 26, no. 9, 1990, pages 1995-1998, --- -/--	1-16

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CAS; PIEPER H. ET AL.: retrieved from STN Database accession no. 112:138679 XP002148693 RN 101513-48-8 abstract & ARZNEIM.-FORSCH., vol. 39, no. 9, 1989, pages 1073-1080, ---	1-4,81
X	DATABASE CHEMABS 'Online! CAS; BAGULEY BRUCE C. ET AL.: retrieved from STN Database accession no. 108:179602 XP002148694 RN 106831-10-1 abstract & EUR. J. CANCER CLIN. ONCOL., vol. 24, no. 2, 1988, pages 205-210, ---	1-7,81
X	DATABASE CHEMABS 'Online! CAS; SARUL E. ET AL.: retrieved from STN Database accession no. 103:123106 XP002148695 RN 98187-77-0 & LATV. PSR ZINAT. AKAD. VESTIS, KIM. SER., vol. 2, 1985, pages 225-228, ---	1-9,12
X	DATABASE CHEMABS 'Online! CAS; WOLLWEBER H. ET AL.: retrieved from STN Database accession no. 101:151540 XP002148696 RN 92114-63-1 abstract & ARZNEIM.-FORSCH., vol. 34, no. 5, 1984, pages 531-542, ---	1-10,12, 81
X	DATABASE CHEMABS 'Online! CAS; DENNY WILLIAM A. ET AL.: retrieved from STN Database accession no. 96:79437 XP002148697 RNS 80260-24-8, 80260-26-0 abstract & J. MED. CHEM., vol. 25, no. 3, 1982, pages 276-315, --- -/--	1-7,81

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CAS; MYSYK D.D. ET AL.: retrieved from STN Database accession no. 92:163637 XP002148698 RN 73320-75-9 & ZH. ORG. KHIM., vol. 15, no. 12, 1979, pages 2499-2502, ---	1-10,12
X	DATABASE CHEMABS 'Online! CAS; ZAITSEVA ET AL.: retrieved from STN Database accession no. 86:43377 XP002148699 RN 61381-98-4 & ZH. ORG. KHIM., vol. 12, no. 9, 1976, pages 1987-1992, -----	1-10,12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The number of theoretical conceivable compounds resulting from the combination of all claimed substituents precludes a comprehensive search of claims 1-71. Claims 72 to 80 which are directed to specific compounds have been fully searched.

Consequently the search, where incomplete, has been based on the examples constantly characterised by the following features: X and Y are in para-positions; X is a one atom chain link NH, S, SO, SO2, O, CO, CH2; Y is NH-SO2; and R2 is a phenyl group (Art. 6 and 15 PCT; Rule 33 PCT; PCT Guidelines III-3.6, 3.7 and 3.12 and VIII-2).

Nota: It appears an inconsistency in claim 69 whith Ar1 as a benzimidazolyl group since it depends also on claim 68 which itself depends up to claim 63 wherein Ar1 should represent a quinolinyl or isoquinoliyl group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/18178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 3784197 A	25-02-1998
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EP 0069585 A	12-01-1983	CA 1169691 A	26-06-1984
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